Management of Colonic Diverticulitis

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Key Messages

- **Computed tomography (CT) diagnosis and clinical sequelae**
  - CT is probably highly accurate to diagnose acute diverticulitis (moderate SoE) and may increase appropriate management versus clinical diagnosis (low SoE). Misdiagnoses on CT may not increase the risk of poor outcomes (low SoE). The significance of incidental findings is unclear.

- **Treatment of patients with acute diverticulitis**
  - **Outpatient versus inpatient management**: Evidence is insufficient to conclude whether or not outpatient (vs. inpatient) management of patients with uncomplicated diverticulitis leads to higher rates of treatment failure, mortality, and emergency surgery. There is low SoE that long-term diverticulitis recurrence rates and elective surgery rates are similar regardless of management setting.
  - **Antibiotics**: There is low SoE that antibiotics for patients with uncomplicated diverticulitis may result in no difference in recurrence risk, quality of life, or need for surgery compared to no antibiotics. Evidence regarding other outcomes and comparing different antibiotic regimens is insufficient.
  - **Interventional radiology**: The evidence is insufficient to make conclusions about benefits or harms of percutaneous drainage.

- **Colonoscopy following an episode of acute diverticulitis**
  - There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis may, ultimately, have similar rates of colorectal cancer (CRC) as those who do not undergo colonoscopy; however, no studies evaluated comparative risks of CRC death.
  - There is low SoE that patients with recent diverticulitis may have an increased likelihood of having undiagnosed CRC or advanced colonic neoplasia (CRC or advanced adenomas).
  - Among people with recent acute diverticulitis, those 50 or older or who had complicated diverticulitis are at increased risk of having CRC (moderate/high SoE), advanced colonic neoplasia (high SoE), or advanced adenoma (low/moderate SoE) on colonoscopy.
  - Colonoscopies after acute diverticulitis rarely have complications or incomplete tests (high SoE).

- **Nonsurgical interventions to prevent recurrent diverticulitis**
  - 5-aminosalicylic acid (5-ASA) neither reduces the risk of recurrence nor causes serious adverse events (both high SoE) Evidence for other interventions is insufficient.

- **Elective surgery to prevent recurrent diverticulitis**
  - For patients with prior complicated or recurrent diverticulitis, elective surgery reduces the risk of recurrent diverticulitis (high SoE). With low to moderate SoE, serious surgical complications included 30-day mortality (0.7%), 30-day readmission (7.3%), and reoperation (5.5%).
Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows: To be included in the final report.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the
scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows: To be included in the final report.
Management of Colonic Diverticulitis

Structured Abstract

**Background.** There remain uncertainties about the effectiveness and harms of various nonsurgical treatment options for acute diverticulitis, clinical consequences of diagnostic imaging, detection strategies for colorectal cancer (CRC) in patients with recent diverticulitis, and preventive options for long-term recurrence. The findings of the review are expected to inform health care providers, policymakers, and patients, and support new guidance on diagnosis, staging, and nonsurgical treatment of acute diverticulitis, and interventions to prevent recurrence, and colonoscopy to evaluate risk of CRC in people with recent acute diverticulitis.

**Methods.** We searched Medline, Cochrane databases, Embase, CINAHL, and ClinicalTrial.gov databases from 1990 through July 11, 2019. We included existing systematic reviews (SR) of computed tomography (CT) test accuracy, randomized controlled trials (RCT), adequately adjusted nonrandomized comparative studies (NRCS), and generally larger single group studies that addressed clinical consequences of CT imaging or harms of interventions.

**Results.** We included 72 primary studies and 2 SRs. With moderate strength of evidence (SoE), CT has high sensitivity (94%) and specificity (99%) to diagnose acute diverticulitis. There is low SoE that CT imaging leads to appropriate management decisions and that misdiagnoses on CT do not result in poor clinical outcomes. The clinical significance of incidental findings is unclear (insufficient). There is also insufficient evidence regarding the test accuracy of grading diverticulitis by CT imaging. For patients with uncomplicated acute diverticulitis, there is low SoE that initial outpatient or inpatient management have similar risks of recurrence or elective surgery, but insufficient evidence regarding risk of treatment failure and other outcomes. Also for patients with uncomplicated acute diverticulitis, there is low SoE that antibiotics do not affect risk of recurrence or quality of life, but may reduce the need for surgery. There is insufficient evidence regarding interventional radiology procedures for complicated acute diverticulitis (e.g., percutaneous drainage). There is low SoE that patients who undergo colonoscopy soon after acute diverticulitis may, ultimately, have similar rates of CRC than those who do not. There is low SoE that patients with recent acute diverticulitis may be at increased risk of CRC compared with the general population. Patients older than 50 years may be at increased risk of CRC (moderate SoE) or premalignant lesions found on colonoscopy (low to high SoE). Colonoscopy after acute diverticulitis rarely results in complications or incomplete procedures (high SoE). 5-ASA does not reduce the risk of recurrence and is not more harmful than placebo (both high SoE). The evidence regarding other nonsurgical interventions to prevent recurrence is insufficient. In patients with prior complicated or recurrent diverticulitis, elective surgery reduces the risk of diverticulitis recurrence (high SoE), but no evidence regarding which patients may benefit most from surgery. Serious surgical complications included 30-day mortality (0.7%), 30-day readmission (7.3%), and reoperation (5.5%) (low to moderate SoE across outcomes).

**Conclusion.** Many of the important questions about which interventions should be used for which patients remain either unanswered or answered with only low SoE. There is a clear need for new high-quality research.
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Evidence Summary

MAIN POINTS

- **Computed tomography (CT) diagnosis and clinical sequelae**
  - CT is probably highly accurate to diagnose acute diverticulitis (moderate SoE) and may increase appropriate management versus clinical diagnosis (low SoE). Misdiagnoses on CT may not increase the risk of poor outcomes (low SoE). The significance of incidental findings is unclear.

- **Treatment of patients with acute diverticulitis**
  - **Outpatient management:** Evidence is insufficient to conclude whether or not outpatient management of patients with uncomplicated diverticulitis leads to higher rates of treatment failure, mortality, and emergency surgery than inpatient management. There is low SoE that long-term diverticulitis recurrence rates and elective surgery rates are similar regardless of management setting.
  - **Antibiotics:** There is low SoE that antibiotics for patients with uncomplicated diverticulitis may result in no difference in recurrence risk, quality of life, or need for surgery compared to no antibiotics. Evidence regarding other outcomes and comparing different antibiotic regimens is insufficient.
  - **Interventional radiology (percutaneous drainage):** The evidence is insufficient to make conclusions.

- **Colonoscopy following an episode of acute diverticulitis**
  - There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis may, ultimately, have similar rates of colorectal cancer (CRC) than those who do not undergo colonoscopy; however, no studies evaluated comparative risks of CRC death.
  - There is low SoE that patients with recent diverticulitis may have an increased likelihood of having undiagnosed CRC or advanced colonic neoplasia (CRC or advanced adenomas).
  - Among people with recent acute diverticulitis, those 50 or older or who had complicated diverticulitis are at increased risk of having CRC (moderate/high SoE), advanced colonic neoplasia (high SoE), or advanced adenoma (low/moderate SoE) on colonoscopy.
  - Colonoscopies after acute diverticulitis rarely have complications or incomplete tests (high SoE).

- **Nonsurgical interventions to prevent recurrent diverticulitis**
  - 5-aminosalicylic acid (5-ASA) neither reduces the risk of recurrence nor causes serious adverse events (both high SoE) Evidence for other interventions is insufficient.

- **Elective surgery to prevent recurrent diverticulitis**
  - For patients with prior complicated or recurrent diverticulitis, elective surgery reduces the risk of recurrent diverticulitis (high SoE). However, there is no evidence regarding which patients would benefit most from elective surgery. With low to moderate SoE, serious surgical complications included 30-day mortality (0.7%), 30-day readmission (7.3%), and reoperation (5.5%).
BACKGROUND

Colonic diverticulitis is caused by inflammation of abnormal outpouchings (diverticula) in the wall of the large intestine. Acute episodes of diverticulitis may be uncomplicated or accompanied by complications such as perforations, peritonitis, abscesses, fistulas, and strictures. Traditional management for patients with uncomplicated diverticulitis includes hospitalization, bowel rest, antibiotics, and intravenous fluids. Complicated diverticulitis may require more invasive interventions, such as surgery or interventional radiology procedures. There remain uncertainties about the effectiveness and harms of various treatment options, preventive options for long-term recurrence, and detection strategies for colorectal cancer (CRC).

PURPOSE

This systematic review evaluates: (1) the accuracy of computed tomography (CT) and harms related to false positive, false negative, and incidental findings on CT imaging; (2) the effectiveness and harms of hospitalization for acute uncomplicated diverticulitis, antibiotics for acute complicated or uncomplicated diverticulitis, and interventional radiology for acute complicated diverticulitis; (3) the need for colonoscopy in people with a history of diverticulitis; and (4) the effectiveness and harms of pharmacologic, nonpharmacologic, and elective surgery to prevent recurrent diverticulitis. The findings of the review are expected to inform health care providers, policymakers, and patients, and support new guidance on diagnosis, staging, and nonsurgical treatment of acute diverticulitis, and interventions to prevent recurrence, and CRC screening in people with a history of diverticulitis.

METHODS


RESULTS

CT: Existing reviews found high sensitivity (94%) and specificity (99%) of CT to diagnose acute diverticulitis (moderate strength of evidence [SoE]). There is low SoE that: (1) CT imaging leads to appropriate management decisions for patients with acute diverticulitis, (2) misdiagnoses on CT do not result in poor clinical outcomes, and (3) incidental findings, although common, have unclear clinical significance. There is insufficient evidence about grading diverticulitis by CT imaging.

Outpatient management of acute diverticulitis: The evidence is insufficient to make conclusions about whether or not outpatient management of patients with uncomplicated diverticulitis leads to higher rates of treatment failure, mortality, and emergency surgery than inpatient management. Adverse outcomes, such as mortality and emergency surgery are
uncommon (3% of patients or fewer), regardless of setting. There is low SoE that long-term diverticulitis recurrence rates and elective surgery rates are similar between the settings.

**Antibiotic treatment of acute diverticulitis:** There is low SoE that antibiotics for patients with uncomplicated diverticulitis do not affect risk of recurrence or quality of life but may reduce the need for surgery over the following year. Evidence regarding death, treatment failure, hospital length of stay, diverticulitis-related morbidities, pain or tenderness, rehospitalization, and adverse events is insufficient to make conclusions. These events are mostly rare. Studies that compared antibiotic regimens each evaluated different regimens. Thus, there is insufficient evidence about their relative effectiveness.

**Interventional radiology:** The evidence is insufficient to make conclusions regarding the potential benefits or harms of percutaneous drainage.

**Colonoscopy:** There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis may, ultimately, have similar rates of CRC than those who do not undergo colonoscopy; however, no studies evaluated comparative risks of CRC death. There is low SoE that, compared with healthy controls, patients with recent acute diverticulitis may be at increased likelihood of finding CRC on colonoscopy. Among these patients, about 2% have CRC, 7% have advanced colonic neoplasia (CRC or advanced adenoma), and between 2% and 3% have specific premalignant lesions (moderate to high SoE). There is also variable (low to high) SoE that older patients (≥50 years) and patients with recent complicated diverticulitis are at particularly high risk of CRC and various premalignant lesions. There is high SoE that procedural complications are rare (fewer than 1% of patients) and that colonoscopy failure rates are also uncommon (3.5%) soon after acute diverticulitis.

**Nonsurgical interventions to prevent recurrent diverticulitis:** There is high SoE that 5-ASA does not reduce the risk of recurrence and is not more harmful than placebo. Evidence for other interventions (rifaximin, combination 5-ASA and rifaximin, combination 5-ASA and probiotics, probiotics, and burdock tea) is too sparse to make conclusions (insufficient). No studies evaluated medical nutrition therapy.

**Elective surgery to prevent recurrent diverticulitis:** There is high SoE that elective surgery reduces the risk of recurrence of diverticulitis among patients with prior complicated or recurrent diverticulitis, but no evidence regarding which patients may benefit most from surgery. There was low to moderate SoE that serious adverse events are uncommon with elective surgery, including that fewer than 1% of patients die postoperatively.

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**LIMITATIONS**

With few exceptions, the evidence base examined in this review for each specific question is based on very few studies or of low SoE. Evidence is particularly sparse for questions related to the benefits and harms of CT scanning for acute diverticulitis, the appropriateness of outpatient management of uncomplicated or mildly complicated diverticulitis, interventional radiology for nonsurgical complicated diverticulitis, and various interventions for prevention of recurrent diverticulitis. In addition, there is very limited evidence regarding which patients might benefit most from (or be most harmed by) the various interventions. Regarding colonoscopy, the studies have not adequately addressed whether patients who undergo colonoscopy after diverticulitis are at decreased risk of dying from CRC compared to patients who forgo colonoscopy.
IMPLICATIONS and CONCLUSIONS

Many of the important questions about which interventions should be used for which patients remain either unanswered or answered with only low SoE.

Prior reviews have demonstrated that CT imaging accurately diagnoses acute diverticulitis. While the clinical implications of false positive, false negative, and incidental findings remain unclear, there is a low SoE that misdiagnoses on CT did not result in poor clinical outcomes. Of note, there is insufficient evidence regarding the test accuracy of clinical staging classifications based on CT imaging.

For selected patients with uncomplicated acute diverticulitis, outpatient management may be as effective as inpatient care. In addition, for patients with uncomplicated diverticulitis, antibiotics may not affect risk of recurrence or quality of life but may reduce the need for surgery. Overall, avoidance of antibiotics appears to be safe. For patients who do receive antibiotics, the evidence is insufficient to guide choice of antibiotic regimen. The evidence is insufficient to assess the clinical value of percutaneous drainage.

Patients with recent episodes of diverticulitis are at increased risk of having undiagnosed CRC or advanced colonic neoplasia, particularly if they are at least 50 years of age or have had complicated diverticulitis. However, there is no evidence regarding whether or not early colonoscopy affects CRC mortality.

5-ASA appears to offer no benefit to patients to reduce the risk of recurrence of diverticulitis. There is insufficient evidence regarding other potential prophylactic treatments. In particular, despite clinical and patient interest, there is no comparative evidence regarding medical nutrition therapies.

Patients with a history of prior complicated or recurrent diverticulitis who undergo elective surgery are at greatly reduced risk of recurrent diverticulitis; however, there is no evidence regarding which patients would most benefit from elective surgery. Postoperative mortality is uncommon, but patients not uncommonly require readmission or reoperation.

The evidence base, particularly for comparisons of interventions is mostly of low strength of evidence (or insufficient or completely lacking). To enable better guidance about best options for patient management, there is a clear need for high-quality research to address the unanswered questions. Ideally, large-scale, multicenter trials should be conducted in unrestricted populations (i.e., without eligibility restrictions that may reduce applicability of findings) with appropriate subgroup analyses and, as needed, analytic methods to account for the inherent differences between people who receive different treatments.
Introduction

Background

Colonic diverticulitis is caused by inflammation of abnormal outpouchings (diverticula) in the wall of the large intestine. The precursor to diverticulitis is diverticulosis, in which the diverticula are not inflamed. They typically are asymptomatic. Overall, about 5 to 10 percent of patients with diverticulosis develop acute diverticulitis, and the number of emergency department admissions for diverticulitis has been increasing over time. Diverticulosis has generally regarded to be a disease affecting the elderly; about 60 percent of people over the age of 60 have diverticulosis. However, recent data have revealed a marked increase in younger patients, with about 30 percent or more of Americans younger than 40 years having diverticulosis and thus being at increased risk for developing acute diverticulitis. Nevertheless, the risk of developing acute diverticulitis rises rapidly with age from 7.1 per 100,000 for those in the 18 to 29 age group, through 113.9 per 100,000 for 50 to 59 year olds, to 263.7 per 100,000 for those over age 80 (per the Nationwide Inpatient Sample from 2000 to 2010). Due to high hospitalization rates and related costs, in the setting of potentially feasible outpatient management, diverticulitis has been prioritized as a measure to compare and reduce variability across national emergency department admission rates.

Symptoms of diverticulitis typically involve acute or subacute lower abdominal pain, often associated with nausea, diarrhea, or constipation. While early studies suggested that diverticulitis is a recurrent disease of a progressive nature, more recent studies in the era of improved medical treatment and more reliable diagnostic imaging suggest the course of diverticulitis is less severe than it was in the past, with fewer episodes of complicated diverticulitis. Nevertheless, about one-quarter of patients have recurrence after a first episode of acute diverticulitis, and even if not complicated, these unpredictable recurrences can be a great source of distress to patients.

Computed tomography (CT) scanning is currently the mainstay for diagnosis of suspected diverticulitis. There are about 200,000 hospital discharges for acute diverticulitis in the U.S. annually, suggesting that several hundred thousand adults are undergoing CT scanning each year to diagnose or rule out acute diverticulitis. The ubiquitous use of abdominal CT has raised concerns about diagnostic errors (whether false positive or false negative) and the potential impact of incidental findings on CTs conducted to rule out or assess diverticulitis (e.g., incidental liver masses that may need invasive or costly workups).

Acute episodes of diverticulitis may be complicated or uncomplicated. Complications are mostly caused by small or large diverticular perforations, which may introduce gut bacteria into the peritoneal space. Complications include abscesses, peritonitis, fistulas, and strictures; complications occur in about 15 to 20 percent of cases of acute diverticulitis. Several schema to classify diverticulitis severity have been published, from the earliest one by Hughes in 1963, to one recently proposed by the European Association for Endoscopic Surgery. Most widely used is the Hinchey Classification, which has been modified to include mild clinical disease, and further updated to reflect CT findings to help not just with diagnosis but also with prognosis. Multiple other classification schemes exist that mostly stage severity, complications, and relapses, or CT findings.

Traditional management for patients with uncomplicated diverticulitis includes bowel rest, antibiotics, and hydration. Treatment may involve hospitalization for intravenous (IV) antibiotics and fluids, and monitoring. In recent years emerging concepts in the pathogenesis from alteration in the gut microbiome, gut dysmotility, and inflammatory rather than infectious etiology has
questioned this established approach. Management of complicated diverticulitis may require more intensive and invasive interventions, including open or laparoscopic surgeries with or without interventional radiology procedures to remove the affected portion of bowel or to drain or cleanse the peritoneal space. Several controversies have emerged with regards to the optimal management of acute diverticulitis. Recent narrative reviews highlighted where current common practices in the management of acute diverticulitis, including medical, surgical, and interventional radiological, may not be supported by the evidence for all patients, including universal hospitalization, use of IV antibiotics, and colectomy and other aggressive surgical procedures for complicated episodes. For example, a recent randomized controlled trial suggested there was no difference in treatment failure between admission and outpatient management with considerable cost savings in the latter group. The duration of antibiotic treatment and the need for antibiotics have been questioned. A recent systematic review (SR) of current strategies for uncomplicated diverticulitis revealed unproven differences in outcomes between observational management and antibiotic therapy and between oral and IV antibiotics.

Due to the increased morbidity and mortality associated with emergent surgery for acute complicated diverticulitis, in the absence of peritonitis, physicians have opted to delay definitive surgical management by employing antibiotics and interventional radiology procedures, such as percutaneous drainage of abscess in appropriate patients; but the supporting evidence for this approach is unclear. There has been an increase in interventional radiology approaches to manage acute complicated diverticulitis, such as percutaneous abscess drainage via ultrasound or CT image-guided catheter placements. Initially reserved for the sickest, highest-risk surgical patients, drainage and antibiotic treatment is now used as definitive treatment to avoid surgery and allow shorter hospital stay and faster recovery.

Patients with a diverticulitis complicated by an abscess have traditionally been offered an interval (non-emergency, elective) colectomy after treatment with antibiotics and possible percutaneous drainage. The rationale for subsequent surgery was to prevent future complications, but recent studies have found that nonsurgical, continued medical treatment of diverticulitis is safe, with low rates of subsequent surgery. More current literature has increasingly revealed that diverticulitis is not a progressive disease as once thought, and that increasing number of episodes do not lead to more complications or the need for urgent operative management. Indeed, studies have found that the greatest risk of free perforation and peritonitis is during the first episode of the disease. Moreover, the risk of recurrence is likely much lower than previously thought. Nevertheless, the rate of elective hemicolecotomies in the U.S. following an episode of acute diverticulitis continues to rise (through 2016), particularly among those between 65 and 79 years old.

The natural course of diverticulitis was once thought to be more severe in younger patients (<50 years) than it is currently believed to be; thus age is no longer used as a criterion to electively operate on younger patients with a history of diverticulitis. In contrast, a lower threshold for both elective and emergency surgical intervention continues to be recommended for immunocompromised patients, such as people with organ transplants, receiving chemotherapy, or with chronic kidney disease.

Strategies to reduce (or eliminate) diverticulitis recurrence have evolved. Despite very low quality of evidence, guidelines recommend high-fiber diets, but no longer recommend avoiding seeds, nuts, and popcorn. Various pharmacologic treatments are used in clinical practice, although uncertainty remains. For example, the 2015 American Gastroenterological
Association guideline recommended against using mesalamine (5-aminosalicylic acid or 5-ASA), an anti-inflammatory agent that is effective for ulcerative colitis.45 There remain unanswered questions regarding the potential adverse consequences of CT imaging (related to false positive tests that may lead to further invasive testing and surgery) to diagnose uncomplicated and complicated diverticulitis. The evidence regarding this potential harm has not been summarized to date.

Another area of controversy includes the appropriateness of performing colonoscopy following a resolved episode of diverticulitis to detect occult colonic malignancy.46 CT features of acute diverticulitis may mimic colon cancer;47 thus professional societies have recommended followup colonoscopy to exclude colon cancer after an episode of acute diverticulitis.48 However, the prevalence of colorectal cancer in this setting has been found to be low for patients with uncomplicated diverticulitis,49 leading some authors to question the need for routine colon evaluation for these patients. The value of CT (or virtual) colonography, noninvasive imaging of the interior lumen of the colon, for colon evaluation in this setting requires more study. Although it may be associated with less pain and improved patient tolerance, its diagnostic accuracy is uncertain.50

Purpose of the Review

The American College of Physicians (ACP) nominated the topic of management of acute diverticulitis to the Agency for Healthcare Research and Quality for SR.51,52 The ACP develops guidelines based on the needs of its members and the internal medicine community.53 The scope of the current SR was developed to support the ACP in its effort to create a new clinical practice guideline that will address diagnosis and staging of acute diverticulitis, nonsurgical treatment of acute diverticulitis, colorectal cancer screening in people with a history of diverticulitis, and interventions to prevent recurrence of acute diverticulitis.

Specifically, (1) the SR summarizes existing SRs on the test accuracy of CT imaging for diagnosis of acute diverticulitis and conducts a de novo review test accuracy for CT staging and of harms related to false positive, false negative, and incidental findings on CT imaging for suspected acute diverticulitis; (2) it addresses effectiveness, comparative effectiveness, and harms of hospitalization for acute uncomplicated diverticulitis, antibiotics use for acute complicated or uncomplicated diverticulitis, and interventional radiology techniques for acute complicated diverticulitis; (3) it reviews the benefits and harms of colonoscopy in people with a history of diverticulitis; and (4) it evaluates pharmacologic, nonpharmacologic, and elective surgical interventions to prevent recurrent diverticulitis. Of note, this review does not evaluate the need for, or the choice of, surgery for the patient with acute diverticulitis.

The intended audience includes guideline developers, clinicians and other providers of care for patients with diverticulitis, healthcare policy makers, and patients.
Methods

Review Approach

The [Redacted] Evidence-based Practice Center conducted this systematic review (SR) based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). This SR also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA),54 A Measurement Tool to Assess Systematic Reviews (AMSTAR 2),55 and any relevant extension statements.

A more detailed version of the SR methodology used can be found in Appendix B.

The topic of this report and preliminary Key Questions (KQs) arose through a process involving the nominators (the American College of Physicians), a panel of Key Informants (KI) and a Technical Expert Panel (TEP), the public, and AHRQ. Initially, the KI panel gave input on the KQs, including the outcomes, to be examined. AHRQ then posted these KQs and solicited public comment through its Effective Health Care (EHC) Program Website and on the Federal Register. No comments were received. The TEP provided high-level content and methodological expertise throughout development of the review protocol. The final protocol is posted on the EHC Website at https://effectivehealthcare.ahrq.gov/products/diverticulitis/protocol on September 12, 2019. We submitted the protocol for registration in PROSPERO in November 2019. On April 29, 2020, PROSPERO published the protocol with registration number CRD42020151246.

Key Questions (KQ)

KQ 1: In CT imaging for the diagnosis or staging of acute diverticulitis,

KQ 1a. What is the test accuracy of CT imaging for the diagnosis or staging of acute diverticulitis?
KQ 1b. What are the effects of CT imaging on clinical outcomes and changes in clinical management?
KQ 1c. What are the downstream outcomes related to false positive or false negative CT readings of acute uncomplicated or complicated diverticulitis
KQ 1d. For patients presenting with acute abdominal pain, with the possibility of acute diverticulitis, what are the downstream outcomes related to incidental findings

• Does the accuracy or do the effects vary by patient characteristics, presentation of illness, or other factors?

KQ 2: What are the benefits and harms of various treatment options for the treatment of acute diverticulitis?

KQ 2a. For patients with acute uncomplicated diverticulitis, what are the effectiveness and harms of hospitalization versus outpatient management of the acute episode?

• Do the effects and harms vary by patient characteristics, presentation or course of illness, or other factors?
KQ 2b. For patients with acute uncomplicated or complicated diverticulitis, what are the effects, comparative effects, and harms of antibiotics?

- Do the effects and harms vary between patients with complicated or uncomplicated diverticulitis?
- Do the (comparative) effects and harms vary by route of administration of antibiotics, type of antibiotic, and duration of course of antibiotics?
- Do the (comparative) effects and harms vary by patient characteristics, presentation or course of illness, or other factors?

KQ 2c. For patients with acute complicated diverticulitis, what are the effects and harms of interventional radiology procedures compared with conservative management?

- Do the effects and harms vary by patient characteristics, presentation or course of illness, or other factors?

KQ 3: What are the benefits and harms of colonoscopy (or other colon imaging test) following an episode of acute diverticulitis?

KQ 3a. What is the incidence of malignant and premalignant colon tumors found by colonoscopy, and what is the incidence of colon cancer mortality among patients undergoing screening?

KQ 3b. What are the procedure-related and other harms of colonoscopy or CT colonography?

KQ 3c. What is the frequency of inadequate imaging due to intolerance or technical feasibility?

- Do the benefits and harms vary by patient characteristics, course of illness, or other factors?

KQ 4: What are the effects, comparative effects, and harms of pharmacological interventions (e.g., mesalamine), non-pharmacological interventions (e.g., medical nutrition therapy), and elective surgery to prevent recurrent diverticulitis?

- Do the (comparative) effects and harms vary by patient characteristics, course of illness, or other factors?

Analytic Framework

Based on discussions with KIs and TEP, we developed analytic frameworks (Appendix A Figures A-1 to A-4). These graphically lay out the populations, interventions, outcomes, and modifiers that pertain to each KQ.

Study Selection

Literature searches were conducted in Medline (via PubMed), the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, CINAHL, and ClinicalTrials.gov, restricted to 1990 through July 11, 2019 [to be updated during peer review]. The search was restricted to recent studies (since 1990) based on important changes in diagnosis
and clinical management of diverticulitis based on increased use of computed tomography (CT) imaging since the 1990s. Additional searches were conducted in ClinicalTrials.gov.

Table 1 presents the major eligibility criteria for each KQ. More detailed criteria are presented in the Appendix. We included randomized controlled trials (RCT), nonrandomized comparative studies (NRCS), single group studies (noncomparative between interventions), and existing SRs.

Table 1. Study eligibility criteria, per Key Question

<table>
<thead>
<tr>
<th>Eligibility Categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ 1: CT imaging</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Adults with suspected or known acute colonic diverticulitis or with acute abdominal pain</td>
</tr>
<tr>
<td>Intervention/Comparator</td>
<td>Abdominopelvic CT scan</td>
</tr>
<tr>
<td></td>
<td>Comparison with other diagnostic imaging test. No comparator necessary.</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>KQ 1a (diagnostic accuracy)</td>
<td>Test accuracy for diagnosis</td>
</tr>
<tr>
<td></td>
<td>Test accuracy for staging</td>
</tr>
<tr>
<td>KQ 1b (clinical outcomes)</td>
<td>Short, medium, and long-term clinical outcomes (e.g., time to resolution)</td>
</tr>
<tr>
<td></td>
<td>Resources (e.g., length of hospital stay)</td>
</tr>
<tr>
<td>KQ 1c (harms)</td>
<td>Harms related to overtreatment (due to false positive CT)</td>
</tr>
<tr>
<td></td>
<td>Harms related to undertreatment (due to false negative CT)</td>
</tr>
<tr>
<td>KQ 1d (incidental findings)</td>
<td>Sequelae related to incidental findings (e.g., unnecessary liver biopsy)</td>
</tr>
<tr>
<td>Design</td>
<td></td>
</tr>
<tr>
<td>KQ 1a: Existing systematic reviews</td>
<td></td>
</tr>
<tr>
<td>KQ 1b-d: Unbiased sampling (eligibility based only on pre-imaging criteria)</td>
<td></td>
</tr>
<tr>
<td>N≥100</td>
<td></td>
</tr>
<tr>
<td>KQ 2 (acute treatments)</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Adults with acute colonic diverticulitis, either complicated or uncomplicated</td>
</tr>
<tr>
<td>Intervention/Comparator</td>
<td></td>
</tr>
<tr>
<td>KQ 2a (hospitalization)</td>
<td>Hospitalization vs. outpatient management (no hospitalization)</td>
</tr>
<tr>
<td>KQ 2b (antibiotics)</td>
<td>Antibiotics (any) vs.</td>
</tr>
<tr>
<td></td>
<td>No antibiotics</td>
</tr>
<tr>
<td></td>
<td>Other antibiotics</td>
</tr>
<tr>
<td></td>
<td>Other antibiotic regimens (e.g., 4 vs. 7 days, oral vs. intravenous)</td>
</tr>
<tr>
<td>KQ 2c (interventional radiology)</td>
<td>Interventional radiology procedure (any) vs.</td>
</tr>
<tr>
<td></td>
<td>No interventional radiology procedure</td>
</tr>
<tr>
<td></td>
<td>Other interventional radiology procedure or technique</td>
</tr>
<tr>
<td></td>
<td>Exclude laparoscopic and other surgical procedures</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Clinical diverticulitis outcomes</td>
<td>E.g., Death, resolution, time to resolution, diverticulitis-related morbidities</td>
</tr>
<tr>
<td></td>
<td>(&quot;complications&quot;), (avoided) procedures/surgery, recurrent diverticulitis</td>
</tr>
<tr>
<td>Other patient-centered outcomes</td>
<td>E.g., Quality of life; functional outcomes; missed work, etc.</td>
</tr>
<tr>
<td>Resources</td>
<td>E.g., Length of hospital stay, return to hospital (or ED), clinic visits</td>
</tr>
<tr>
<td>Harms</td>
<td>KQ 2a: hospital-based infections, other major harms</td>
</tr>
<tr>
<td></td>
<td>KQ 2b: Adverse events attributable to antibiotics (major), including C diff infection</td>
</tr>
<tr>
<td></td>
<td>KQ 2c: Adverse events related to procedures. E.g., major bleeds and infections</td>
</tr>
<tr>
<td>Eligibility Categories</td>
<td>Criteria</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
</tr>
</tbody>
</table>
| Design                 | RCT: N≥10  
NRCS: Mostly restrict to studies that use analytic methods to minimize selection bias.  
N≥30  
Single group studies: N≥100 (for harms only) |

**KQ 3 (colonoscopy)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with history of resolved acute diverticulitis</th>
</tr>
</thead>
</table>
| Intervention/Comparator | Elective colonoscopy  
No comparator necessary  
No colonoscopy (or other colon imaging)  
Other colon imaging (complete or partial) |

| Outcomes | Colorectal cancer  
Colorectal cancer death  
High-risk colonic premalignant lesions: adenoma with high-grade dysplasia; adenoma  
≥10 mm, villous adenoma, serrated polyp, ≥3 adenomas/patient  
Tolerance, feasibility, procedure completion, technical adequacy  
Harms/adverse events attributable to procedure |

**KQ 4 (recurrence prevention)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with history of resolved acute diverticulitis</th>
</tr>
</thead>
</table>
| Intervention/Comparator | KQ 4a: Nonsurgical interventions, including pharmacologic treatments and nonpharmacologic interventions (e.g., medical nutrition therapy)  
Vs. no intervention or vs. other nonsurgical intervention  
KQ 4b: Elective surgery (exclude delayed surgery for acute diverticulitis)  
Vs. no surgery  
Not comparisons of surgery types or approaches  
Exclude natural history studies or undefined/unspecified interventions or comparators |

| Outcomes | Clinical diverticulitis outcomes  
E.g., Death, recurrent diverticulitis  
Surgery-related clinical outcomes  
E.g., Stoma placement (avoidance)  
Other patient-centered outcomes  
E.g., Quality of life; functional outcomes; missed work, etc.  
Resources  
E.g., Length of hospital stay, return to hospital (or ED), clinic visits  
Harms  
Major surgical adverse events: Clavien-Dindo Grade II (require medical intervention), Grade III (require surgical intervention), Grade IV (organ dysfunction), Grade V (death) |

| Design | RCT: N≥10  
NRCS: Restrict to adjusted analyses (as per KQ 2)  
N≥30  
Single group studies (for harms only): N≥200 |

Abbreviations: C diff = Clostridioides difficile, CT = computed tomography, ED = emergency department, KQ = Key Question, NRCS = nonrandomized comparative study, RCT = randomized controlled trial.

**Risk of Bias Assessment**

We evaluated each study for risk of bias and methodological quality. Because we included a variety of study designs, we incorporated items from three different existing commonly-used tools and tailored the set of items for each study design.

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^ Restrict to studies that use modeling or other analytic methods to minimize selection bias (due to inherent differences between people who receive one or the other intervention) or that restrict study eligibility criteria such that comparisons being made are between patients with similar presentations. However, allow crude (unadjusted) comparisons of long-term outcomes under the assumption that characteristics during acute diverticulitis that were associated with treatment choice would not have a major impact on long-term outcomes. (NRCS that do not meet these criteria were assessed as possibly eligible single group studies.)
For RCTs, we used all the items from the Cochrane Risk of Bias tool,\textsuperscript{56} including randomization and allocation concealment methodology; blinding; completeness of data reporting; and selective reporting.

For NRCSs, we used specific elements from the ROBINS-I Tool\textsuperscript{57} related to confounding and selection bias. We also used items from the Cochrane Risk of Bias and NHLBI tools that were not specific to randomized trials.

For single group studies, we used the items from the above mentioned tools that related to participant loss to followup, incomplete outcome data, selective reporting, and adequacy of descriptions of study eligibility criteria, interventions, and outcomes.

**Data Synthesis and Analysis**

Within the main report, data are summarized either in succinct tables that focus on outcome, interventions, and comparative (when applicable) results or in forest plots or succinct summary tables (for most topics). Appendix D contains the succinct summary tables for the antibiotics Key Question because of their large number and length. The rest of Appendix D includes the more detailed, study-level results for each topic. Appendix C contains detailed tables that describe study and participant characteristics, intervention (and comparator) details, outcomes (and definitions), and arm- and comparison-level results. Appendix C also includes tables providing study-level risk of bias assessments.

When feasible and appropriate, we conducted random effects model pairwise meta-analyses. Details are in Appendix B. Of note, for harms data related to KQ 4 (elective surgery), we meta-analyzed adverse event rates (proportions) when two or more studies reported sufficiently similar adverse events. The goal of these meta-analyses was to allow concise presentation of the adverse event results data; thus, we did not restrict these meta-analyses based on the similarities of the investigated surgeries or on the statistical heterogeneity among included studies (the differences in adverse event rates). To indicate the heterogeneity across studies, we also report the range of adverse event rates across studies.

**Grading the Strength of the Body of Evidence**

We evaluated the strength of evidence (SoE) addressing each major analysis for each KQ. We graded the SoE as per the AHRQ Methods Guide.\textsuperscript{58, 59} For each SoE assessment, we considered the number of studies, the study limitations, the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, and other limitations (particularly sparseness of evidence). Based on these assessments, we assigned a SoE rating as being either high, moderate, low, or insufficient to estimate an effect. Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one study were deemed to have insufficient evidence to allow a conclusion.
Results

The Results Chapter is organized by Key Question (KQ) and, as pertinent, by subquestion. High-level summary tables and forest plots describing overall findings across studies are included in the main report. More detailed summary tables describing each study and other detailed information are in Appendixes C and D. Each section (either by KQ or by subsection) has a list of Key Points that includes the strength of evidence (SoE) for the conclusions. This is followed by the findings and a summary of findings with a SoE table.

Overview of the Evidence Base Addressing All Key Questions

The literature database searches yielded 14,061 citations. We found 673 citations to retrieve for further screening. Ultimately 71 primary studies (reported in 85 articles) and two systematic reviews (SR) were eligible and included. The most frequent reasons for exclusion of articles were: existing SR (n=90), single group study of elective surgery with N<500 (KQ 4, n=59), no specific intervention (n=49; e.g., natural history study), secondary publication with no unique data of interest (n=49), not intervention of interest (n=38), computed tomography (CT) study without clinical or management outcomes (KQ 1, n=37), surgery for acute diverticulitis (n=34), article not available (n=33; most are likely conference abstracts), and single group studies of interventions with N<100 (n=31). See literature flow figure in Appendix C (Figure C-1) and the list of rejected studies in Appendix B for more details.

Key Question 1. Computed Tomography (CT)

Key Points

- Existing SRs have demonstrated very high sensitivity (94%) and specificity (99%) of CT to diagnose acute diverticulitis (moderate SoE)
- There is insufficient evidence to evaluate diverticulitis staging criteria.
- Based on 2 studies, CT imaging led to appropriate surgical or medical management of acute diverticulitis (low SoE); however, no studies have compared CT imaging to no imaging.
- Based on 3 studies, misdiagnoses on CT (i.e., false positive or negative CT scans) did not clearly result in poor clinical outcomes (low SoE)
- Based on 2 studies of CT imaging performed in the emergency department for acute abdomen, incidental findings (unrelated to the abdominal pain) were common, but it remains unclear what the clinical significance (either beneficial or harmful) of these findings are (low SoE)

Findings Pertaining to CT Imaging

Key Question 1a. Test Accuracy of CT Imaging

Diagnosis of Acute Diverticulitis

Two existing systematic reviews have summarized the evidence for diagnostic test accuracy of CT for patients with suspected diverticulitis.60,61 Despite the span of time between the two publications (2008 to 2014), both reviews included the same eight primary studies, which had
been published between 1990 and 2005. The later review (Andeweg 2014) conducted its literature search in PubMed, Embase, and the Cochrane Library of Systematic Reviews through December 2013. This SR did not report its funding source. The earlier review (Laméris 2008) also searched CINAHL. This SR was funded by a Dutch nonprofit organization. Both reviews included studies that evaluated the diagnostic performance of CT (and other imaging tests) in patients with suspected acute colonic diverticulitis. None of the primary studies reported their funding source. However, Andeweg 2014 excluded two German language studies because they “did not report a consecutive series of patients”; although, they did grade them as being of moderate quality. However, while the two articles do not provide much detail regarding their selection of participants, in our determination the included patients were likely enrolled consecutively. In addition, Andeweg 2014 used a substandard meta-analytic method that treated sensitivity and specificity as independent measures. Therefore, we recalculated their analyses with bivariate random effects model meta-analysis, which appropriately jointly meta-analyzes sensitivity and specificity. Laméris 2008 used this method.

The original primary studies each included between 33 and 150 patients (684 total) whose mean ages ranged from 51 to 71 years (and which included 19 to 98 year olds). Women accounted for 54 to 72 percent of the samples. Prevalence rates of final diagnosis of acute diverticulitis and of complicated diverticulitis varied, ranging from 36 to 68 percent with acute diverticulitis and 10 to 60 percent of those with diverticulitis having complicated disease. Laméris 2008 judged the overall quality of the evidence to be “moderate” based on the QUADAS tool, primarily due to issues with the reference standard. Notably, the reference standard was not independent of the index test (final diagnosis was based, in part, on CT findings) and a lack of uniform verification (only a subset of individuals had surgical or colonoscopic verification of diagnosis).

With or without the two German studies, pooled sensitivity and specificity were high and similar. Summary sensitivity was, with all studies, 94 percent (95% CI 87 to 97) and specificity was 98.9 percent (95% CI 90 to 99.9). Excluding the two German studies yielded a summary sensitivity of 92 percent (95% CI 84 to 97) and specificity of 99.2 percent (91 to 99.9). The summary receiver operator characteristics (ROC) graph is depicted in Figure 1.
Each circle represents an included study, with the size of the circles correspond to the relative sample sizes of each study. The squares indicates the summary sensitivities and specificities. The curve represents the summary receiver operating characteristics (ROC) curve. The black box and ROC curve represent the meta-analysis of all eight studies. The grey box and ROC curve exclude the two studies excluded by Andeweg 2014, which are indicated by grey circles with X’s in them.

Staging of Acute Diverticulitis

Only one study evaluated the test accuracy of a clinical classification system to stage acute diverticulitis and reported sufficient data to estimate all test accuracy statistics (e.g., both sensitivity and specificity). However, the study evaluated a staging system that is not commonly used in clinical practice in the U.S.
Jurowich 2011 evaluated the Hansen and Stock (H&S) classification system,\textsuperscript{71} which was initially published in 1999 in German only.\textsuperscript{72} The H&S system does not appear to have been published in English. According to the Jurowich 2011 article,\textsuperscript{72} it is commonly used in Germany.

The H&S system includes the following categories:

- **Type 0** Asymptomatic diverticulosis (not further discussed here)
- **Type I** Uncomplicated diverticulitis, first episode
  - Potential intestinal wall thickening and/or enhancement of pericolic fatty tissue; sometimes no morphologic features visible on CT
- **Type IIA** Complicated “phlegmonous diverticulitis”
  - Type I criteria and edema/phlegmonous inflammation, but no free air
- **Type IIB** Complicated “covered perforation”
  - Type IIA criteria and air inclusions, corresponding with abscesses
- **Type IIC** Complicated “free perforation”
  - Free air, free intra-abdominal contrast media escape, and/or free fluid
- **Type III** Uncomplicated diverticulitis, recurrent
  - Apparently, the same CT criteria as Type I, but with knowledge of two or more episodes of recurrence (presumably including the current episode)

As suggested by these criteria, the H&S grading system is a “CT-based predictive system,” not a CT-only grading system; it also includes clinical assessment. Furthermore, an unreported number of patients staged as Type IIC (perforated diverticulitis with diffuse peritonitis) did not receive CT imaging, but instead went for immediate emergency surgery. In addition, an unreported number of patients with uncomplicated diverticulitis (Type I) were imaged with ultrasound, not CT.

The final diagnosis (reference standard) was based on operative findings or recovery with conservative therapy (initially diagnosed as Type I or IIA). Patients initially classified as Type IIA who had recovery within 24 hours of conservative therapy were given a final classification of Type I (uncomplicated) diverticulitis. For patients who were reclassified postoperatively as uncomplicated diverticulitis, no distinction was made between Type I (who did not require surgery, per protocol) and Type III (who did require surgery, per protocol).

Given the incomplete assessment by CT, the inclusion of non-CT information in the grading, and the imprecise reference standard, the study was deemed to be of poor methodological quality (to assess CT for grading the severity of acute diverticulitis).

The study evaluated 318 consecutive patients (including 11 patients with acute diverticulitis who had preoperative misdiagnoses of acute appendicitis, incarcerated hernia, or ileus) with acute sigmoid diverticulitis. The patients’ median age was 64 years (range 26 to 97) and 57 percent were men.

Among these patients, 242 underwent surgery; only these patients are included in the test accuracy analyses. Details about the initial and final staging of the evaluated patients and our approach to analyzing the reported data are presented in Appendix D.

As summarized in Table 2, test sensitivity and specificity of the H&S categories varied widely depending on stage and whether one considers each stage as an individual classification or as a maximum or minimum threshold. The largest discrepancy between initial and postoperative staging was among the 83 evaluated patients with Type IIA (“phlegmonous
diverticulitis”), 64 percent of whom were misclassified (53% were reclassified to Type IIB, 11% were reclassified to Type I or Type III [the article did not distinguish the two categories]). The article did not adequately report whether patients who underwent surgery based on initial staging all required the surgery (based on postoperative findings). The study also did not report on the clinical sequelae of patients with Types IIA or IIB diverticulitis who did not undergo recommended surgery.

Table 2. Test accuracy of initial staging, per Jurowich 2011

<table>
<thead>
<tr>
<th>Stage vs. all others</th>
<th>Final +</th>
<th>Final −</th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>46</td>
<td>8</td>
<td>78.0</td>
<td>95.6</td>
<td>85.2</td>
<td>93.1</td>
</tr>
<tr>
<td>Not III</td>
<td>13</td>
<td>175</td>
<td>(65.3, 87.7)</td>
<td>(91.6, 98.1)</td>
<td>(74.2, 92.0)</td>
<td>(89.3, 95.6)</td>
</tr>
<tr>
<td>2A</td>
<td>30</td>
<td>53</td>
<td>93.8</td>
<td>74.8</td>
<td>36.1</td>
<td>98.7</td>
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<tr>
<td>Not 2A</td>
<td>2</td>
<td>157</td>
<td>(79.2, 99.2)</td>
<td>(88.3, 98.0)</td>
<td>(30.6, 42.1)</td>
<td>(89.3, 99.7)</td>
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<tr>
<td>2B</td>
<td>71</td>
<td>7</td>
<td>58.2</td>
<td>94.2</td>
<td>91.0</td>
<td>68.9</td>
</tr>
<tr>
<td>Not 2B</td>
<td>51</td>
<td>113</td>
<td>(48.9, 67.1)</td>
<td>(84.4, 97.6)</td>
<td>(83.0, 95.5)</td>
<td>(64.1, 73.3)</td>
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<tr>
<td>2C</td>
<td>27</td>
<td>0</td>
<td>93.1</td>
<td>100</td>
<td>100</td>
<td>99.1</td>
</tr>
<tr>
<td>Not 2C</td>
<td>2</td>
<td>213</td>
<td>(77.2, 99.2)</td>
<td>(98.3, 100)</td>
<td>(NA)</td>
<td>(96.6, 99.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage max vs. higher stages</th>
<th>Final +</th>
<th>Final −</th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
<tbody>
<tr>
<td>III</td>
<td>46</td>
<td>8</td>
<td>78.0</td>
<td>95.6</td>
<td>85.2</td>
<td>93.1</td>
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<tr>
<td>2A or 2B or 2C</td>
<td>13</td>
<td>175</td>
<td>(65.3, 87.7)</td>
<td>(91.6, 98.1)</td>
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<td>(89.3, 95.6)</td>
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<td>2A or III</td>
<td>86</td>
<td>51</td>
<td>94.5</td>
<td>66.2</td>
<td>62.8</td>
<td>95.2</td>
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<td>5</td>
<td>100</td>
<td>(87.6, 98.2)</td>
<td>(58.1, 73.7)</td>
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<td>99.1</td>
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<td>(77.2, 99.2)</td>
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</table>

<table>
<thead>
<tr>
<th>Stage min vs. lower stages</th>
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<th>Final −</th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A or 2B or 2C</td>
<td>175</td>
<td>13</td>
<td>95.6</td>
<td>78.0</td>
<td>93.1</td>
<td>85.2</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>46</td>
<td>(91.6, 98.1)</td>
<td>(65.3, 87.7)</td>
<td>(89.3, 95.6)</td>
<td>(74.2, 92.0)</td>
</tr>
<tr>
<td>2B or 2C</td>
<td>100</td>
<td>5</td>
<td>66.2</td>
<td>94.5</td>
<td>95.2</td>
<td>62.8</td>
</tr>
<tr>
<td>III or 2A</td>
<td>51</td>
<td>86</td>
<td>(58.1, 73.7)</td>
<td>(87.6, 98.2)</td>
<td>(89.4, 97.9)</td>
<td>(57.3, 68.0)</td>
</tr>
<tr>
<td>2C</td>
<td>27</td>
<td>0</td>
<td>93.1</td>
<td>100</td>
<td>100</td>
<td>99.1</td>
</tr>
<tr>
<td>III or 2A or 2B</td>
<td>2</td>
<td>213</td>
<td>(77.2, 99.2)</td>
<td>(98.3, 100)</td>
<td>(NA)</td>
<td>(96.6, 99.8)</td>
</tr>
</tbody>
</table>

Estimates for test accuracy of different evaluated stages.

The section Stage vs. all others compares each individual stage with not that stage (both more and less severe stages). The section Stage max vs. higher stages evaluates each stage and lesser severity stages compared with more severe stages. The section Stage min vs. lower stages evaluates each stage and greater severity stages compared with less severe stages.

Abbreviations: Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value.

Key Questions 1b to 1d. Sequelae of CT imaging

We found only five studies that reported either clinical sequelae related to CT imaging for patients suspected of acute diverticulitis or incidental findings on abdominal CTs performed in the emergency department for acute abdomen. Overall, the studies did not report or analyze clear, clinically relevant results data pertinent to the Key Questions and were deemed to be of poor methodological quality as pertains to reporting of sequelae of CT imaging. In particular, none of the studies compared CT-guided care versus care without CT guidance. Andeweg 2011

B Note that this is identical to III vs. Not III.
C Note that this is the inverse of III vs. Not III (or III vs. 2A or 2B or 2C). I.e., Sn and Sp, and PPV and NPV, are flipped.
D Note that this is the inverse of 2A or III vs. 2B or 2C. I.e., Sn and Sp, and PPV and NPV, are flipped.
E Note that this is identical to 2C vs. Not 2C.
reported no funding for their study\textsuperscript{73} and Waqas 2014 reported no commercial funding for their study.\textsuperscript{74} The other three studies did not report funding source.\textsuperscript{75-77} All studies are summarized in Table 3 and Appendix C.

### Table 3. CT imaging sequelae and incidental findings

<table>
<thead>
<tr>
<th>Study, PMID</th>
<th>N</th>
<th>CT Errors</th>
<th>Good Clinical Sequelae</th>
<th>Poor Clinical Sequelae</th>
<th>Incidental Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martín Arévalo, 2007 17883294</td>
<td>102</td>
<td>CRC: 2/86 (2.3%)\textsuperscript{F}</td>
<td>14/26 spared surgery (that was presumptively indicated by clinical diagnosis) (17% of all) 2/58 received (presumably appropriate) surgery (that was presumptively not indicated by clinical diagnosis) (2.4%)</td>
<td>2/86 missed CRC diagnosis, but unclear that this resulted in actual poor clinical sequelae.</td>
<td>None reported</td>
</tr>
<tr>
<td>Salem 2005, 16108882</td>
<td>81</td>
<td>1 FN</td>
<td>6 with (incorrect) clinical diagnosis of diverticulitis were correctly diagnosed with other conditions by CT\textsuperscript{G} 2 with missed clinical diagnosis of diverticulitis managed correctly after CT\textsuperscript{H} 2 mis-staged clinically managed correctly after CT\textsuperscript{I}</td>
<td>1 FN (on CT) died prior to surgery\textsuperscript{J}</td>
<td>None reported</td>
</tr>
<tr>
<td>Andeweg 2011, 21346548</td>
<td>287</td>
<td>None reported</td>
<td>NR</td>
<td>No unnecessary surgeries (poor clinical sequelae) were reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Kelly 2015, 25576049</td>
<td>1155</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>74 (6.4%) &quot;indeterminate&quot; requiring further workup\textsuperscript{K}</td>
</tr>
<tr>
<td>Waqas 2014, 24475484</td>
<td>290</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9 new\textsuperscript{L} &quot; worrisome&quot; 73 new &quot;indeterminate&quot;</td>
</tr>
</tbody>
</table>

\textsuperscript{F} 2 erroneous diagnoses of diverticulitis that intraoperatively proved to be sigmoid colorectal cancer complicated by an abscess.

\textsuperscript{G} Dissecting aortic aneurysm, left adrenal tumor, left pyonephrosis, metastatic colorectal cancer, acute appendicitis, and inflammatory bowel disease.

\textsuperscript{H} 1 clinically diagnosed with acute abdomen had perforated diverticulitis on CT (managed surgically). 1 clinically diagnosed with intra-abdominal bleeding had (uncomplicated, implicitly) diverticulitis on CT (managed medically).

\textsuperscript{I} 1 with a small bowel obstruction missed on clinical examination, 1 who did not have a clinically diagnosed perforation.

\textsuperscript{J} Diagnosis made post-mortem.

\textsuperscript{K} 24: clinically silent occult neoplasms (pancreas, colorectal, kidney, liver, sarcoma, lung, gallbladder, gastric, gynecologic), 5: <50 years old, 6: deemed early local disease with good potential for curative resection, 7: adrenal adenoma, 5: colorectal polyps, 2: perforated diverticulitis/mass, 1: complex renal cyst, 1: thickening/lesion of lower esophagus, 34: benign clinically insignificant findings.

\textsuperscript{L} Not previously known per clinical notes or previous imaging studies.

\textsuperscript{M} Only 3/9 new worrisome incidental findings received a recommendation by radiologist for further workup; all 3 had a change in clinical management based on the CT findings. Of the remaining 6 with no recommendation for further workup, only 2 had a change in clinical management.

\textsuperscript{N} 23/73 new indeterminate incidental findings received a recommendation by radiologist for further workup; of these
Key Question 1b. Effects of CT Imaging on Clinical Outcomes and Clinical Management (Good Clinical Sequelae)

Two studies reported specific good clinical sequelae related to abdominal CT imaging of people presenting with clinical diagnoses of acute diverticulitis or acute abdomen, not including implied good clinical sequelae based on accurate diagnosis of diverticulitis (or other cause of acute abdomen).

Martín Arévalo 2007 evaluated 102 adults with clinical diagnoses of acute diverticulitis; although the eligibility criteria were vague. All received abdominal CT, although contrast was used only if an abscess was clinically suspected. Among these 102 patients, 84 were diagnosed with acute diverticulitis by CT imaging, of whom 81 percent had uncomplicated diverticulitis, 10 percent each had small abscesses, large abscesses, or diffuse peritonitis. The authors reported that 14 people were spared surgery among 26 people for whom surgery for complicated diverticulitis was indicated based on clinical criteria (17% of all with diverticulitis). Another 2 patients received surgery that was not indicated based on clinical criteria alone (2.4% of all with diverticulitis); it was implied that the surgeries were appropriate.

Salem 2005 evaluated 211 adults with acute abdomen, 48 of whom had acute diverticulitis (although the diagnostic criteria were not reported). Among these patients, 81 had abdominal CTs (with contrast)—16 of whom had a final diagnosis of diverticulitis—and 130 did not have CT imaging—32 of whom had a final diagnosis of diverticulitis. The authors report that among those who received CT imaging, 6 had incorrect clinical diagnoses of diverticulitis that were, implicitly, managed correctly due to the CT diagnoses. These patients had, by CT imaging, a dissecting aortic aneurysm, an adrenal tumor, pyonephrosis, metastatic colorectal cancer, acute appendicitis, and inflammatory bowel disease. In addition, 2 patients were correctly diagnosed with diverticulitis on CT, which had been missed on clinical examination. One of these patients was clinically diagnosed with intra-abdominal bleeding but had diverticulitis that was successfully managed medically. The other patient was clinically diagnosed with “acute abdomen” and was found to have perforated diverticulitis on CT. This patient was managed surgically; it is unclear whether clinical sequelae were altered for this patient. A further two patients had their diverticulitis clinically mis-staged; one had a small bowel obstruction that had been missed on clinical examination and one did not have a perforation that had been diagnosed on clinical examination. The first patient received surgical treatment (although it was not reported what the pre-CT surgical plan was); the second patient was treated medically.

Key Question 1c. Outcomes Related to False Positive or False Negative CT Readings (Poor Clinical Sequelae)

Three studies reported on poor clinical sequelae related to erroneous readings of abdominal CTs. These included the two studies described above (for good clinical sequelae) and a third study of patients hospitalized for acute abdomen.

As noted, Martín Arévalo 2007 evaluated 102 adults with clinical diagnoses of acute diverticulitis; 84 had final diagnoses of acute diverticulitis, mostly (81%) uncomplicated. The authors reported that 2 patients had false positive abdominal CTs (for diverticulitis) and were

16 had a change in clinical management based on the CT finding. Of the 50 with new indeterminate incidental findings with no recommendation for a further workup, 1 had a change in clinical management.
found to have colorectal cancer at surgery. Both had sigmoid colon cancers complicated by an abscess. However, the article does not report whether there were any actual poor clinical sequelae based on the missed CT diagnoses.

Also as noted above, Salem 2005 evaluated 211 adults with acute abdomen, 48 of whom had acute diverticulitis. The study compared 81 patients who had abdominal CTs (16 with a final diagnosis of diverticulitis) and 130 who did not have CT imaging (32 with a final diagnosis of diverticulitis). Among the 81 who had a CT, the authors report that one patient had a false negative CT reading (for diverticulitis) who subsequently died. The diagnosis was made on post-mortem examination; although the article did not report on an investigation into the role of the misdiagnosis in the patient’s death. Among the 130 people who did not have a CT, no (poor) clinical sequelae or misdiagnoses were noted related to the lack of CT imaging.

Andeweg 2011 evaluated 287 people who were hospitalized with acute abdominal pain who did not require immediate surgery, although the eligibility criteria were vague. The study was designed to create a predictive algorithm for diagnosis of diverticulitis, not to report on clinical sequelae related to CT imaging. All patients had an abdominal CT for “suspected diverticulitis” or “left lower quadrant pain”. In their sample, 124 had acute left-sided diverticulitis, 31 of who had surgical management. The authors reported that there were no unnecessary surgeries (i.e., no poor clinical sequelae based on CT diagnoses).

Key Question 1d. Clinically important Incidental Findings

Our search yielded two studies that reported on incidental findings on abdominal CT imaging performed for acute abdomen in the emergency department. None of the three studies discussed for KQ 1c or 1d that reported on clinical sequelae related to CT imaging reported on incidental findings.

Kelly 2015 reported on 1155 patients who received an emergency abdominal CT in the Emergency Department of a tertiary referral hospital. The study did not report on CT or final diagnoses (including diverticulitis). The authors reported that 74 patients (6.4%) had “indeterminate” findings on CT that required further workup, 34 of which were determined to be “benign, clinically insignificant findings.” Of the remaining 40 patients (3.5%), 24 (2.1%) had “clinically silent occult neoplasms”: pancreas, colorectal, kidney, liver, sarcoma, lung, gallbladder, gastric, and gynecologic. Five of these patients were younger than 50 years of age and six of the cancers were deemed to be “early local disease with good potential for curative resection”. Among the remaining patients, 7 had adrenal adenomas, 5 colorectal polyps, 2 perforated diverticulitis, 1 complex renal cyst, and 1 a thickening/lesion of the lower esophagus. It is unclear why the 2 patients found to have complicated diverticulitis were classified as having incidental findings on their emergency abdominal CT. The study did not report on downstream clinical sequelae of the incidental findings on CT imaging.

Waqas 2014 reported on 290 patients who had abdominopelvic CTs for nontraumatic acute abdominal pain in the Emergency Department. The study did not report on CT or final diagnoses (including diverticulitis). The study described the numbers of patients who had “indeterminate” and “worrisome” findings on CT, how many of these resulted in suggestions by the radiologist for further workup, and how many patients had changes in clinical management. The study reported that 139 patients (48%) had incidental findings, but most were previously known per clinical notes or previous imaging studies. The study reported 9 (3.1%) patients with new worrisome incidental findings. It was not reported what these findings were. For only 3 of the patients did the radiologist recommend further workup; all 3 had a change in clinical
management due to the worrisome incidental finding. Of the 6 patients with worrisome CT findings but without a recommendation for further workup, only 2 had a subsequent change in clinical management. The study further reported that 73 patients (25%) had new worrisome CT findings, for whom 23 received a recommendation for further workup. Of these 16 had a change in clinical management based on the CT finding. Of the 50 people with a worrisome CT finding without a recommendation for further workup, only one had a change in clinical management. The study did not report on downstream clinical sequelae of the incidental findings on CT imaging (beyond receiving a workup).

Summary of Evidence Pertaining to CT Imaging

Based on meta-analysis of multiple, consistent studies, there is moderate SoE that CT imaging of patients with suspected acute colonic diverticulitis has very high sensitivity (94%; 95% CI 87% to 97%) and very high specificity (99.2%; 95% CI 81% to 99.9%). The primary deficiency of studies was that the reference standard was not definitive for most patients (since surgical or colonoscopic diagnoses were not available).

Based on two studies, there is low SoE that abdominal CT imaging may lead to appropriate surgical or medical management and that for some patients, at least, appropriate management might not have occurred without CT imaging. However, neither study compared CT imaging to no imaging.

Based on three studies, there is low SoE regarding poor clinical sequelae related to diverticulitis-related misdiagnoses on CT. The studies did not clearly identify that the poor clinical outcomes were direct consequences of the misdiagnoses (i.e., that better outcomes would have been likely with correct diagnoses).

Based on two studies, there is low SoE that among patients receiving emergency abdominal CTs for nontraumatic acute abdomen in the emergency department, incidental findings may not be uncommon. The larger study found that important incidental clinical diagnoses are made on CT. The smaller study found that radiologists do not suggest further workup for most new indeterminate or worrisome incidental findings on CT. Neither study reported on clinical outcomes or sequelae related to the incidental findings. Full evidence profiles are in Table 4.
Table 4. Evidence profile for CT imaging for acute diverticulitis

<table>
<thead>
<tr>
<th>Topic</th>
<th>No. Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Conclusion statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT accuracy</td>
<td>8 (684)</td>
<td>Moderate*</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>Sn 94%, Sp 99%</td>
</tr>
<tr>
<td>Good clinical sequelae</td>
<td>2 (183)</td>
<td>High</td>
<td>Consistent</td>
<td>Precise</td>
<td>Indirect</td>
<td>Sparse</td>
<td>Low</td>
<td>CT resulted in appropriate management of diverticulitis</td>
</tr>
<tr>
<td>Poor clinical sequelae</td>
<td>3 (470)</td>
<td>High</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Indirect</td>
<td>None</td>
<td>Low</td>
<td>CT may have resulted in some cases of inappropriate management due to misdiagnosis</td>
</tr>
<tr>
<td>Incidental findings</td>
<td>2 (1445)</td>
<td>High</td>
<td>Consistent</td>
<td>Precise</td>
<td>Indirect</td>
<td>None</td>
<td>Low</td>
<td>Incidental findings are common, although their clinical significance is unclear</td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography, N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence, unadj = unadjusted.

* Per Laméris 2008, 60 based on QUADAS tool.70

- Unclear that good sequelae would not have occurred without CT. No clear concept of good clinical sequelae in articles.
- Unclear that poor sequelae would not have occurred without CT. No clear concept of poor clinical sequelae in articles.
- The clinical course of sequelae of the incidental findings was poorly reported and analyzed.
Key Question 2. Medical Management of Acute Diverticulitis

Key Question 2a. Outpatient Management of Acute Diverticulitis

Key points

- Adverse outcomes were rare, regardless of outpatient or inpatient management: death 0.2%, emergency surgery 1.3%. The evidence is insufficient regarding comparison of management settings.
- Outpatient treatment led to inconsistent findings on treatment failure in two studies, with no statistically significant difference observed in one RCT and a benefit in favor of outpatient care (despite adjustment for patient morbidity) in one NRCSs (insufficient SoE).
- There is no evidence of a difference in long-term recurrence (low SoE) or rate of elective surgery (low SoE) regardless of inpatient or outpatient management.

Findings Pertaining to Outpatient Management

One small RCT\textsuperscript{29} and five NRCSs\textsuperscript{78-82} evaluated outpatient treatment protocols compared to inpatient care for the management of an acute uncomplicated diverticulitis episode. With the exception of Moya 2012, all the NRCSs were retrospective. The average age was similar across studies, with participants in their mid to late 50s with between 37 and 64 percent being male. Although we sought to include only NRCS with adjusted analyses, we made some exceptions, providing justifications. The RCT was funded by nonindustry; funding for all five NRCSs was not reported. Appendix C Table C-2a-1 provide detailed descriptions of the six studies.

The RCT (Biondo 2014) enrolled 132 participants with uncomplicated diverticulitis who were responsive to initial treatment in the ED (i.e., improvement of pain and fever), were able tolerate oral intake, and were willing to continue treatment at home under supervision. Initial treatment in the ED included a first dose of antibiotics (IV amoxicillin/clavulanate or ciprofloxacin)

The prospective NRCS (Moya 2012) studied adults with uncomplicated diverticulitis who could tolerate oral intake and had adequate family and social support to be discharged to outpatient care. The study used a pre-post interrupted time series design around a hospital policy change regarding discharging patients. Although not formally adjusted, we included this study since it is unlikely that patients in each time period systematically differed from each other and no differences were observed for baseline predictors.

The remaining four NRCSs (Bolkenstein 2018, Lorente 2013, Ünlü 2013, and Joliat 2017) used a retrospective design to compare outpatient to inpatient treatment protocols. Bolkenstein 2018 studied adults with a first episode of uncomplicated diverticulitis who did not receive antibiotics (2 weeks prior to, or 24 hours after presentation to the hospital). For a single outcome, the study adjusted for the fact that patients in the inpatient group tended to be sicker than those discharged to outpatient care at baseline (i.e., higher levels C reactive protein (CRP), white blood cell counts, and symptoms of fever and nausea).

We derived long-term outcomes (average 17- to 60-month followup) from three NRCSs that were unadjusted despite baseline imbalances. Patients treated inpatient were generally sicker. We determined that the baseline imbalances are relatively unlikely to confound outcomes more than a year later. The first of these studies, Lorente 2013, studied adults with uncomplicated
diverticulitis who met the hospitals’ criteria to be treated at home (i.e., tolerated oral intake, adequate family and social support, absence of comorbidities). Ünlü 2013 studied adults treated for their first episode of uncomplicated diverticulitis and compared outcomes of those discharged to outpatient care within 24 hours of presenting to the hospital to those admitted to inpatient care. Joliat 2017 studied adults with uncomplicated or mild complicated diverticulitis and assessed long-term outcomes via a patient survey.

The RCT was low risk of bias for randomization, blinding of outcome assessors (due to objective nature of the outcomes), and incomplete outcome data but high risk of bias for blinding of participants and personnel, and unclear risk of bias for selective outcome reporting (Appendix C Table C-2a-2). The NRCSs had high risk of bias for confounding as all but one study reported crude event proportions rather than an effect estimate adjusted for important confounders (full risk of bias in Appendix C Table C-2a-3). The NRCSs had low risk of bias for participant selection with the exception of one study (Joliat 2017) that recruited patients and assessed their outcomes by means of a survey. Full study results and risk of bias assessment are in Appendices C and D.

**Mortality**

Death was rare. Only 2 of 1009 (0.2%) died due to acute diverticulitis across three studies (Biondo 2014, Bolkenstein 2018, and Ünlü 2013).

**Treatment failure**

The RCT (Biondo 2014) and the adjusted NRCS (Bolkenstein 2018) reported treatment failure (Table 5).²⁹ ⁸²

The RCT (Biondo 2014) found that treatment failure occurred at similar rates between inpatient- and outpatient-treated groups and was uncommon (~5%). Their findings yielded an imprecise comparison (OR 0.74, 95% CI 0.16 to 3.43). Treatment failure was defined as persistence, increase, or recurrence of abdominal pain and/or fever, inflammatory bowel obstruction, need for radiological abscess drainage or immediate surgery due to complicated diverticulitis, need for hospital admission, and mortality during the first 60 days after discharge.

In contrast, the adjusted NRCS (Bolkenstein 2018) found that patients treated as outpatient had significantly fewer treatment failures compared to inpatient (adjusted OR 0.41, 0.20 to 0.83). Treatment failure was defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotic treatment, operative intervention, or percutaneous abscess drainage within 30 days after initial presentation.

<table>
<thead>
<tr>
<th>Table 5. Outpatient versus inpatient management: Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Treatment failure</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, PMID = Pubmed identifier.

⁸ Defined as persistence, increase, or recurrence of abdominal pain and/or fever, inflammatory bowel obstruction, need for radiological abscess drainage or immediate surgery due to complicated diverticulitis, need for hospital admission, and mortality during the first 60 days after discharge.

² Defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotic treatment, operative intervention, or percutaneous abscess drainage within 30 days after initial presentation.

Adjusted for sex, age, ASA score > 2, no rebound tenderness, C-reactive protein (mg/L)
**Emergency Surgery**

The RCT (Biondo 2014) and Moya (the pre-post study) both reported that no patients (of 208 total) required emergency surgery, regardless of treatment assignment. Given the small numbers of patients reported on, however, this suggests a relatively wide 95 percent confidence interval (0% to 3.7%).

**Recurrence**

The four NRCSs that reported unadjusted analyses of recurrence had average followup ranging from approximately 8 to 55 months. 78-81 Recurrence rates across the studies, mostly undefined, tracked with average followup time (6.6% at about 8 mo, 78 19% at 17 mo, 79 24% at 48 mo, 81 and 41% at about 55 mo). By meta-analysis (Figure 2), the summary OR found no evidence of a difference in recurrence rates between outpatient and inpatient management (summary OR 0.85, 95% CI 0.62 to 1.17). Although, in these unadjusted analyses, it was likely that patients treated inpatient had more severe episodes of acute diverticulitis, there was no suggestion that these patients were more likely to have recurrence in the long-term.

**Figure 2. Meta-analysis of outpatient versus inpatient management: Recurrence of diverticulitis**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outpt</th>
<th>Inpt</th>
<th>OR (95% CI)</th>
<th>Followup</th>
<th>Recurrence Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moya 2012</td>
<td>2/32</td>
<td>3/44</td>
<td></td>
<td>0.92 (0.14, 5.81)</td>
<td>~8 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Lorente 2013</td>
<td>15/90</td>
<td>10/46</td>
<td></td>
<td>0.82 (0.34, 1.94)</td>
<td>17 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Ünlü 2013</td>
<td>22/118</td>
<td>53/194</td>
<td></td>
<td>0.70 (0.40, 1.20)</td>
<td>48 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Julian 2017</td>
<td>40/98</td>
<td>70/169</td>
<td></td>
<td>0.99 (0.62, 1.56)</td>
<td>~55 mo</td>
<td>New Sx &gt;1 mo</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.62, 1.17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, I² = measure of statistical heterogeneity (% of heterogeneity not due to random chance), Inpt = inpatient management, mo = months, NR = not reported, OR = odds ratio, Outpt = outpatient management, P_{Het} = statistical heterogeneity P value, Sx = symptoms (of acute diverticulitis).

**Elective surgical treatment**

In three NRCSs with an average follow-up ranging from approximately 8 to 55 months there was no statistically significant difference in elective surgical treatment between outpatient and inpatient management across studies. 78, 80, 81 Two studies had elective surgery rates of 4 percent at about 8 months (Moya 2012) and 48 months (Ünlü 2013); in the third study, 16 percent had elective surgery during about 55 months of followup. By meta-analysis (Figure 3), the summary OR found no evidence of a difference in rates of elective surgery between outpatient and inpatient management (summary OR 0.76, 95% CI 0.42 to 1.37).
Quality of Life

The RCT (Biondo 2014) reported on quality of life and found no difference in physical (P=0.59) and mental health (P=0.99) scales of the SF-12 between the outpatient and inpatient arms at 2 months (Table 6).

Table 6. Outpatient versus inpatient management: Quality of life

<table>
<thead>
<tr>
<th>Study Year</th>
<th>PMID</th>
<th>Outcome</th>
<th>Time</th>
<th>Arm</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Difference</th>
<th>Reported P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biondo 2014 23732265</td>
<td>SF-12 physical</td>
<td>2 mo</td>
<td>Outpatient</td>
<td>66</td>
<td>50.3 (7.2)</td>
<td>0.7 (-2.0, 3.4)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inpatient</td>
<td>66</td>
<td>49.6 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SF-12 mental</td>
<td>2 mo</td>
<td>Outpatient</td>
<td>66</td>
<td>53.0 (8.6)</td>
<td>0.4 (-2.7, 3.5)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inpatient</td>
<td>66</td>
<td>52.6 (9.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abx = antibiotic, CI = confidence interval, ED = emergency department, IV = intravenously, mo = month, NR = not reported, PMID = Pubmed identifier, RCT = randomized controlled trial, SD = standard deviation, wk = week.

Summary of Evidence Pertaining to Outpatient Versus Inpatient Management

For patients with uncomplicated diverticulitis, the evidence comparing outpatient versus inpatient management is inconclusive (insufficient) about the difference among in risk of death, treatment failure, need for emergency surgery, or in quality of life (Table 7), but it does not suggest increased risk of adverse outcomes with outpatient management. With low SoE, the studies suggest there may be no differences in rates of long-term recurrence or elective surgery regardless of outpatient versus inpatient management.
## Table 7. Evidence profile for outpatient versus inpatient management of uncomplicated acute diverticulitis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Conclusion statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 (1009)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding outpatient vs. inpatient. Rare event</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2 (697)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Unclear</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient</td>
<td>No conclusion regarding outpatient vs. inpatient</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>2 (208)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding outpatient vs. inpatient. Rare event</td>
</tr>
<tr>
<td>Recurrence (~8-55 mo)</td>
<td>4 (791)</td>
<td>High</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>Unadjusted</td>
<td>Low</td>
<td>No difference found unadj OR 0.85 (0.62, 1.17)</td>
</tr>
<tr>
<td>Elective surgery (~8-55 mo)</td>
<td>3 (655)</td>
<td>High</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>Unadjusted</td>
<td>Low</td>
<td>No difference found unadj OR 0.76 (0.42, 1.37)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>1 (132)</td>
<td>Low</td>
<td>N/A</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding outpatient vs. inpatient</td>
</tr>
</tbody>
</table>

Abbreviations: N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence, unadj = unadjusted.
Key Question 2b. Antibiotics for Acute Diverticulitis

Key points
- Overall, for patients with uncomplicated or mild diverticulitis, the evidence does not support that there are differences in most clinically important differences between either use of antibiotics or not or in choice of antibiotic regimens
  - Specifically, studies found no differences in risk of recurrence and quality of life (low SoE). The risk of surgery at 6 to 12 months after the episode of acute diverticulitis may be lower among patients who received antibiotics, but the finding was highly nonsignificant.
  - Evidence for comparative rates of death, treatment failure, length of hospital stay, diverticulitis-related morbidities, pain or tenderness, rehospitalization, and adverse events is insufficient to make conclusions, largely due to sparse events.
- Although seven studies have compared antibiotic regimens, each evaluated a different comparison (of antibiotics, durations, or routes); therefore, the data are overall insufficient. However, in general, no evidence of differences in clinical outcomes were found for different regimens.

Findings Pertaining to Antibiotics
Overall, 12 studies addressed the use of antibiotics in patients with acute diverticulitis. These included eight RCTs and four NRCSs. All NRCSs reported multivariable-adjusted comparisons. From the NRCSs, we include only those short-term outcomes that were analyzed by multivariable regression. To be consistent with other reviewed topics, we allowed unadjusted analyses of long-term outcomes under the assumption that inherent differences between those patients who received different regimens (in NRCSs) would not be confounded with long-term outcomes.

Across the studies, there were comparisons of antibiotics and no antibiotics (including placebo) and of different antibiotic regimens (including either different antibiotics or different durations of treatment).

One RCT (Schug-Pass 2010) was industry-funded. Three RCTs and one NRCS were funded by nonindustry sources, including the AVOD (Antibiotika Vid Okomplicerad Divertikulit) and DIABOLO (Diverticulitis: Antibiotics or Close Observation) trials, the RCT by Ribas 2010, and the NRCS by Hjern 2007. The other studies did not report industry funding.

In contrast with other sections, because of the large number of comparisons and outcomes evaluated regarding antibiotics, the summary tables (with basic results) are located at the start of Appendix D.

Antibiotics Versus No Antibiotics
Three RCTs in seven reports28, 31, 32, 83-86 and two NRCSs87, 88 compared antibiotics with either placebo or no intervention. Appendix C Tables C-2b-1 to C-2b-5 describe the characteristics of the five studies. The numbers of enrolled participants across the five studies comparing antibiotics with placebo or no antibiotics ranged from 125 to 623. The average ages of participants ranged from 37 to 62 years.

Two RCTs (AVOD and Kim 2019) compared antibiotics with placebo in CT-confirmed acute uncomplicated diverticulitis. In AVOD, the treating clinicians were allowed to choose the
antibiotics to be administered. All patients had left-sided diverticulitis; about 40 percent had recurrent diverticulitis. Broad-spectrum antibiotics were commonly used, and treatment was initiated with intravenous (IV) followed by oral antibiotics. All patients had acute lower-abdominal pain with tenderness, fever, and increased white blood cell (WBC) counts or C-reactive protein (CRP). Kim 2019 compared a combination of IV cephalosporin and metronidazole with placebo in patients with modified Hinchey stage 1a (per Wasvary, uncomplicated) right-sided diverticulitis (the study was conducted in South Korea, where right sided diverticulitis is predominant). Because of the demographic, clinical, and prognostic differences between left- and right-sided diverticulitis, further descriptions of the Kim 2019 study are separated out and findings are not combined with findings of studies of left-sided diverticulitis.

The third RCT (DIABOLO) did not include a placebo group, but compared IV amoxicillin/clavulanate with no antibiotics in patients with modified Hinchey stage 1a or 1b (per Wasvary, uncomplicated or complicated with pericolic or mesenteric abscess <5 cm) or “mild” left-sided acute diverticulitis (per Ambrosetti criteria). For all participants, this was their first episode of diverticulitis.

The two NRCSs (Hjern 2007 and de Korte 2012) compared antibiotic treatment with no antibiotics for a minimum of 7 days. Hjern 2007 evaluated a combination of IV cephalosporin and metronidazole, followed by oral quinolone and metronidazole. de Korte 2012 was a multicenter NRCS, in which antibiotic regimens differed across centers. All patients in both NRCSs had acute mild sigmoid (left-sided) diverticulitis that had been treated conservatively. In Hjern 2007 about 30 percent had a previous episode of diverticulitis. Such patients were included in the de Korte 2012 study, but the numbers were not reported.

Details of the risk of bias assessment for all studies are in Appendix C. All three RCTs had adequate sequence generation and allocation concealment. Kim 2019 blinded participants, providers, and outcome assessors, but AVOD and DIABOLO did not. All three RCTs had low levels of loss to followup. Both the NRCSs adjusted for possible confounding and had low risk of bias in selection of participants into the study, but the outcome assessors were not masked. Both NRCSs had low levels of loss to followup.

Mortality

AVOD and DIABOLO reported on mortality (Appendix D Table D-2b-1). All estimates were imprecise or near imprecise. In DIABOLO, diverticulitis-mortality at 24 months was uncommon (0.8%, total), thus the comparison between groups was imprecise (OR 0.33, 95% CI 0.03 to 3.15). In AVOD, only one of 623 patients (total) died at 30 days, but in very long-term followup (11 years), about 10 percent of patients died in both groups (OR 1.06, 95% 0.60 to 1.86).

Treatment Failure

Two RCTs reported on treatment failure, but one was conducted in patients with left-sided and one in patients with right-sided diverticulitis, and each defined the outcome differently (Appendix D Table D-2b-1). DIABOLO reported recovery as return to normal bowel function at 6 months, which we inverted for treatment failure. Patients with first episode of left-sided diverticulitis treated with amoxicillin/clavulanate had nonsignificantly lower rates of treatment failure than patients not treated with antibiotics (OR 0.61, 95% CI 0.33 to 1.13). Median times to recovery in the two groups were 12 days (IQR 7 to 30) and 14 days (IQR 6 to 35), respectively, which were not significantly different.
Kim 2019 defined treatment failure as nonrecovery and/or readmission after 10 days of treatment. In patients with right-sided diverticulitis, the comparison of treatment failure between combination cephalosporin and metronidazole and placebo was imprecise (OR 0.34, 95% CI 0.03 to 3.35).

**Length of Hospital Stay**

All three RCTs reported on length of hospital stay (Appendix D Table D-2b-2). The two RCTs of patients with left-sided diverticulitis (AVOD and DIABOLO) had conflicting findings. AVOD found a mean difference (MD) of 0 days. In contrast, DIABOLO found a statistically significantly shorter length of stay in the antibiotics group compared with the no antibiotics group (2 vs. 3 days, P=0.006).

The RCT of right-sided diverticulitis (Kim 2019) found a mean difference (MD) of 0 days between antibiotics versus placebo.

**Rehospitalization**

DIABOLO reported on the outcome of rehospitalization for diverticulitis and, separately, rehospitalization for diverticulitis-related complications, at various time-points (Appendix D Table D-2b-1). No statistically significant differences in rate of rehospitalization were found at 6 and 24 months, although both estimates tended to favor amoxicillin/clavulanate versus placebo (OR 0.64, 95% CI 0.39 to 1.05 at 6 months; OR 0.71, 95% CI 0.44 to 1.15 at 24 months).

**Surgery for Diverticulitis**

Two RCTs reported on the outcome of having elective surgery for diverticulitis (6 to 12 months later) (Appendix D Table D-2b-1 to D-2b-3). DIABOLO focused on elective surgery at 6 months and reported an OR of 0.36 (95% CI 0.10 to 1.38) comparing amoxicillin/clavulanate with no antibiotics. AVOD focused on sigmoidectomy at 12 months and reported an OR of 0.33 (95% CI 0.07 to 1.63) comparing antibiotics with no antibiotics.

**Recurrence**

All five studies reported on recurrence of diverticulitis; two within 12 months (short-term recurrence) and four beyond 12 months (long-term recurrence) (Appendix D Table D-2b-1).

One RCT (DIABOLO) reported recurrence at 6 months. The between-group effect size was imprecise and near the null. In this trial, all participants had no prior episodes of diverticulitis.

Two RCTs (AVOD and DIABOLO) and two NRCSs (Hjern 2007 and de Korte 2012) reported on long-term (≥12 months) recurrence in patients with left-sided diverticulitis (Figure 4). Each study had an imprecise comparison, but across studies, the summary OR for recurrence was 1.06 (95% CI 0.70 to 1.43; $I^2=0\%$), suggesting no evidence of a difference in the rate of long-term recurrence with or without antibiotics. Each of these trials included participants with and without prior episodes of diverticulitis.

AVOD also reported that long-term recurrence at 11 years was similar between patients with or without antibiotics (OR 1.00, 95% CI 0.70 to 1.43).

The RCT of right-sided diverticulitis (Kim 2019) reported diverticulitis at 6 or more weeks and found a between-group effect size was imprecise and near the null.
Figure 4. Meta-analysis of antibiotics versus no antibiotics/placebo: Long-term recurrence of left-sided diverticulitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotics</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
<th>F/up</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVOD</td>
<td>46/292</td>
<td>47/290</td>
<td>0.97 (0.62, 1.51)</td>
<td>≥12 mo</td>
</tr>
<tr>
<td>DIABOLO</td>
<td>36/241</td>
<td>35/227</td>
<td>0.96 (0.58, 1.59)</td>
<td>24 mo</td>
</tr>
<tr>
<td>Hjern 2007</td>
<td>NR/118</td>
<td>NR/193</td>
<td>1.03 (0.61, 1.74)</td>
<td>30 mo</td>
</tr>
<tr>
<td>de Korte, 2012</td>
<td>12/81</td>
<td>14/191</td>
<td>2.04 (0.90, 4.63)</td>
<td>50 mo</td>
</tr>
<tr>
<td>Overall (P = 0%, P_Het = 0.43)</td>
<td></td>
<td></td>
<td>1.06 (0.81, 1.39)</td>
<td></td>
</tr>
</tbody>
</table>

| AVOD    | 88/281      | 86/275  | 1.00 (0.70, 1.43) | 11 yr |

Abbreviations: CI = confidence interval, F/up = Follow up, OR = odds ratio, P_Het = P value of test for statistical heterogeneity.

Diverticulitis-Related Morbidities

Two RCTs (AVOD and DIABOLO) described diverticulitis-related morbidities, such as abscess, fistula, stenosis, and obstruction (Appendix D Table D-2b-1). AVOD compared multiple antibiotics with placebo, and DIABOLO compared combination of amoxicillin/clavulanate with no intervention. Regardless of these varied interventions, both studies reported that these morbidities occurred in 3 percent of patients or fewer, regardless of intervention. No evidence of differences with or without antibiotics was evident, although in AVOD, 0.9 percent of patients receiving placebo developed abscesses as opposed to none of those on antibiotics (P=0.08).

Pain or Tenderness

Two RCTs reported on pain or tenderness outcomes (Appendix D Table D-2b-2).

As a short-term outcome (1 to 5 days), AVOD reported no significant differences in acute pain by visual analogue scale (VAS). However, they reported a small, statistically significant worse tenderness score with antibiotics (MD 0.2, 95% CI 0.01 to 0.39; on a 4-point scale). DIABOLO also found no difference in pain, assessed as experiencing pain of at least 4 on VAS within 10 days (OR 0.99, 95% CI 0.60 to 1.46).

In the long term, AVOD reported on three types of pain. All effect sizes were imprecise, including likelihood of severe periodic pain at 12 months, and chronic pain at both 12 months and 11 years.

Quality of Life

Two RCTs reported on quality of life at various time points (Appendix D Table D-2b-2). DIABOLO reported mean quality of life scores over 3, 6, 12, and 24 months, with adjustment for baseline scores, using three general health-related quality of life instruments: the EuroQoL (EQ)-5D, the Short Form-36 (SF-36), and the Gastrointestinal Quality of Life Index (GIQLI). For each instrument and at each time point, quality of life was similar when comparing combination amoxicillin/clavulanate with no antibiotic use.
AVOD reported quality of life at 11 years of followup using the EQ-5D. However, the items in the tool were rare events among the patients, so evaluations each of the five domains were imprecise (anxiety/depression, mobility, pain/discomfort, self-care, and usual activities).

Adverse Events

Only AVOD reported on adverse events (Appendix D Table D-2b-10), but reported an imprecise estimate of differences in “any adverse event,” which actually occurred more frequently among those on placebo.

Comparisons Between Various Antibiotic Regimens

Appendix D Tables D-2b-1 to D-2b-3 describes the characteristics of the seven studies that compared various antibiotic regimens. These included five RCTs (Kellum 1992,91 Ridgway 2009,92 Ribas 2010,93 Schug-Pass 2010,30 and Park 201994) and two NRCSs (Scarpa 201595 and Etzioni 201096). Comparisons were either between antibiotics (or combinations of antibiotics), between different routes of administration of the same antibiotic(s), or between different doses of the same antibiotic(s). As for the comparison of antibiotics versus placebo, results from the Park 2019 RCT are separated out and not combined with evidence pertaining to left-sided diverticulitis.

Each study evaluated a different comparison of antibiotic regimens. They compared:

- Kellum 1992 (RCT): combination gentamicin and clindamycin vs. cefoxitin
- Ridgway 2009 (RCT): combination ciprofloxacin and metronidazole, IV vs. oral
- Ribas 2010 (RCT): amoxicillin/clavulanate, IV then oral vs. IV only
- Schug-Pass 2010 (RCT): ertapenam, 4 days vs. 7 days
- Scarpa 2015 (NRCS): IV antibiotics (various), ≤5 days vs. 6-14 days
- Etzioni 2010 (NRCS): two comparisons
  - combination fluoroquinolone and metronidazole vs. other antibiotics
  - any antibiotic: <10 days, 10-13 days, and ≥14 days
- Park 2019 (RCT of right-sided diverticulitis): combination cephalosporin and metronidazole, 1 day vs. 4 days

All RCTs and NRCSs enrolled patients with image-proven acute diverticulitis. Kellum 1992, Ribas 2010, Schug-Pass 2010, and Etzioni 2010 included all patients with diverticulitis. Ridgway 2008 and Scarpa were restricted to patients with uncomplicated (Hinchey I17 or modified Hinchey 0 [clinically mild] or Ia [confined inflammation]20) diverticulitis. Park 2019 included patients with right-sided diverticulitis exclusively (in South Korea).

Appendix C includes the findings of our assessment of risk of bias in all the RCTs and NRCSs. Four RCTs (Kellum 1992, Ridgway 2009, Ribas 2010, and Park 2019) used appropriate methods for random sequence generation and allocation concealment, while one RCT (Schug-Pass 2010) was unclear on these details. Among the RCTs, only Park 2019 blinded patients. All five RCTs had low levels of loss to followup. Among the NRCSs, Etzioni 2010 conducted appropriate adjustment for potential confounding, but Scarpa 2015 reported only unadjusted analyses. Thus, we included only long-term outcomes from Scarpa 2015 (>12 month recurrence). Both NRCSs had low risk of bias in selection of participants into the study and had low levels of loss to followup.

The numbers of participants enrolled in the RCTs and NRCSs ranged from 50 to 176. The average ages of the patients ranged from 41 to 68 years. Ribas 2010, an RCT, reported that 32
percent of participants had experienced previous episodes of diverticulosis. Other studies either did not report on prior episodes or excluded patients with prior episodes.

**Treatment Failure**

Two RCTs (Ribas 2010 and Ridgway 2008) and one NRCS (Etzioni 2010) reported on treatment failure in patients with left-sided diverticulitis, but definitions of the outcome differed. In all studies, comparisons between antibiotic regimens were imprecise with OR estimates close to 1.00 (Appendix D Tables D-2b-1 to D-2b-3). Ribas 2010 defined treatment failure as persistent pain (within 8 days) or not getting discharged on the expected day. Ridgway 2008 defined treatment failure as readmission within 30 days of completing antibiotic treatment. The Etzioni 2010 NRCS defined treatment failure as either nonelective hospitalization or evaluation in an emergency department within 60 days.

The RCT of right-sided diverticulitis (Park 2019) defined treatment failure as readmission within 30 days of completing antibiotic treatment. The comparison between 1- and 4-day combination cephalosporin and metronidazole provided an imprecise estimate of differences in treatment failure, with the OR estimate close to 1.00.

**Surgery for Diverticulitis**

Two RCTs (Kellum 1992 and Schug-Pass 2010) reported on the outcome of surgery for diverticulitis (Appendix D Table D-2b-1). In Kellum 1992, 6 of 30 patients on cefoxitin had surgery after 6 weeks, while none of 21 patients on combination gentamicin and clindamycin did, but due to the overall small number of patients the estimate of OR was nonsignificant and near imprecise (OR 11.4, 95% CI 0.61 to 215). The comparison between 7- and 4-day courses of ertapenem for up to 12 month elective surgery by Schug-Pass 2010 was also near-imprecise, but nominally favoring the shorter, 4-day, course (OR 1.31, 95% CI 0.57 to 3.04).

**Length of Hospital Stay**

One RCT (Schug-Pass 2010) reported that patients on a 7-day course of ertapenem had a longer mean hospital or intensive care unit stay than patients on a 4-day course (9.7 vs. 7.8 days; MD 1.9 days, 95% CI 0.70 to 3.10) (Appendix D Table D-2b-2).

**Recurrence of Diverticulitis**

One RCT (Schug-Pass 2010) and one NRCS (Scarpa 2015) reported on the outcome of recurrence of diverticulitis, both at 1 year or later (Appendix D Table D-2b-1). All comparisons, though, were imprecise.

**Diverticulitis-Related Morbidities**

Schug-Pass 2010 reported on rates of abscesses, interenteric fistulas, and postinflammatory stenoses at 1 year comparing patients who had received 7-day versus 4-day courses of ertapenem (Appendix D Tables D-2b-1 to D-2b-3). Rates of each morbidity were less than 3 percent and were similar between the groups.

**Pain or Tenderness**

Ridgway 2008 reported that Wexford tenderness scores at 3 days were similar between patients who had received IV and oral combinations of ciprofloxacin and metronidazole (MD −0.06, 95% CI −0.50 to 0.38; on a 0 to 4 scale) (Appendix D Tables D-2b-1 to D-2b-3).
Adverse Events
Schug-Pass 2010 reported on the outcomes of any adverse event, serious adverse events, major allergic reactions, and headaches within 12 months, comparing patients who had received 7-day and 4-day courses of ertapenem (Appendix D Table D-2b-3). Rates of each outcome were 5 percent or fewer between groups.

Summary of Evidence Pertaining to Antibiotics
Despite there being 12 comparative studies overall, and five studies specifically comparing use of antibiotics to placebo (or no antibiotics), the evidence base is generally too sparse or inconsistent to make strong conclusions about the value of antibiotics for patients with uncomplicated or mild diverticulitis. Two of these studies were conducted in patients with right-sided acute diverticulitis (in South Korea).

As summarized in the evidence profile (Table 8), there is insufficient evidence regarding the relative value of antibiotics to affect the most pertinent clinical outcomes of death, treatment failure, length of hospital stay, diverticulitis-related morbidities, pain and tenderness, rehospitalization, or adverse events. Largely, this was due to sparse events or only a single study with evidence, making estimates highly imprecise or inconclusive. There is, however, low SoE that both recurrence rates and quality of life may be similar regardless of use of antibiotics. Similarly, with low SoE, there is no evidence of a difference in risk of surgery at 6 to 12 months, but the two studies that evaluated this outcome both found that about 3-times as many patient who were not given antibiotics had surgery than those given placebo, but with wide confidence intervals. It is unclear whether risk of recurrence or future surgery (or effect on quality of life) may differ between patients being treated for a first-time or recurrent episode of acute diverticulitis.

Seven studies compared different antibiotic regimens in patients with acute diverticulitis. However, each compared different sets of regimens, either different antibiotics (3 studies); different, largely nonoverlapping comparisons of durations of treatment (4 studies); and different routes (1 study). In addition to the problem of only a single study evaluating any given comparison, clinical outcomes were generally sparse within studies, resulting in highly imprecise comparisons of regimens. Thus, the only difference found was that a 7-day course of ertapenem resulted in a shorter length of hospital stay (by about 2 days) than a 4-day course. The full evidence profile is in Table 8.
Table 8. Evidence profile for antibiotics for acute left-sided diverticulitis

<table>
<thead>
<tr>
<th>Topic</th>
<th>Outcome</th>
<th>No. Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Conclusion statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abx vs. no Abx</td>
<td>Death</td>
<td>2 (1151)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse events</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo. Rare event.</td>
</tr>
<tr>
<td>Treatment failure(^V)</td>
<td>Treatment failure</td>
<td>1 (528)</td>
<td>Low</td>
<td>N/A</td>
<td>Imprecise</td>
<td>Indirect(^W)</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo</td>
</tr>
<tr>
<td>Length of hospital stay(^X)</td>
<td>Length of hospital stay</td>
<td>2 (1151)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>Rehospitalization</td>
<td>1 (528)</td>
<td>Moderate</td>
<td>N/A</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo</td>
</tr>
<tr>
<td>Surgery at 6-12 months</td>
<td>Surgery at 6-12 months</td>
<td>2 (1110)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Low</td>
<td>No evidence of a difference, but possible trend toward lower risk with antibiotics OR 0.33 (0.07, 1.63)(^Y)</td>
</tr>
<tr>
<td>Recurrence(^Z)</td>
<td>Recurrence</td>
<td>4 (1624)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Precise</td>
<td>Indirect(^AA)</td>
<td>None</td>
<td>Low</td>
<td>No evidence of a difference Summary OR 1.06 (0.81, 1.39)</td>
</tr>
<tr>
<td>Diverticulitis-related morbidities</td>
<td>Diverticulitis-related morbidities</td>
<td>2 (1151)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse events</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo</td>
</tr>
<tr>
<td>Pain/tenderness</td>
<td>Pain/tenderness</td>
<td>2 (1052)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient</td>
<td>No conclusion regarding antibiotic vs. placebo</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Quality of life</td>
<td>2 (732)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse, per analysis</td>
<td>Low</td>
<td>No evidence of a difference</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Adverse events</td>
<td>1 (1197)</td>
<td>Moderate</td>
<td>N/A</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion comparing antibiotic regimens</td>
</tr>
<tr>
<td>Various Abx regimens</td>
<td>All</td>
<td>7 (1405)</td>
<td>Moderate</td>
<td>N/A</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse, per analysis(^BB)</td>
<td>Insufficient</td>
<td>No conclusion comparing antibiotic regimens</td>
</tr>
</tbody>
</table>

Abbreviations: Abx = antibiotics, LOS = length of stay, MD = mean difference, N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

\(^U\) The two trials of right-sided diverticulitis (Kim 2019 and Park 2019) are omitted. Evidence pertaining to right-sided diverticulitis is insufficient due to sparseness of studies. Footnotes indicate which outcomes were reported by the studies of right-sided diverticulitis.

\(^V\) One study provided insufficient evidence about antibiotics vs. placebo in right sided diverticulitis.

\(^W\) The study described treatment failure at 6 months followup.

\(^X\) One study provided insufficient evidence about antibiotics vs. placebo in right sided diverticulitis.

\(^Y\) AVOD finding at 12 months. DIABOLO had similar finding at 6 months (OR 0.36, 95% CI 0.10, 1.38).

\(^Z\) One study provided insufficient evidence about antibiotics vs. placebo in right sided diverticulitis.

\(^AA\) Time points ranged from 12 to 50 months. AVOD also found similar results at 11 years.

\(^BB\) Each study evaluated a different comparison of antibiotic regimens.
Key Question 2c. Interventional Radiology for Acute Diverticulitis

Key Points
- The evidence is insufficient to make conclusions regarding the potentially beneficial effects of percutaneous drainage for treatment of acute complicated diverticulitis.
- No comparative studies have reported on procedural adverse events.

Findings Pertaining to Interventional Radiology
Only two studies, both retrospective NRCSs, reported the effects and harms of interventional radiology (specifically, percutaneous drainage) compared with conservative management (no percutaneous drainage) in patients with acute complicated diverticulitis.\textsuperscript{97, 98} The two NRCSs, with a total of 483 participants, are summarized in Appendix C Tables C-2c-1 to C-2c-3; results are in Appendix D Table D-2c-1.

Lambrichts 2019, for which the funding source was not reported, studied 447 adults with modified Hinchey category Ib or II acute complicated diverticulitis (with confined or distant abscesses, per Wasvary\textsuperscript{18}). Three-quarters of the patients received percutaneous drainage. Patients were on average in their early 60s. Approximately two-thirds of patients (62\% of patients receiving drainage and 72\% not receiving it) were undergoing their first episode of diverticulitis. Of note, at baseline, patients receiving percutaneous drainage had higher levels of inflammatory parameters, such as CRP and WBCs, were more likely to have modified Hinchey II (distant abscesses) diverticulitis, and had larger abscesses than patients not receiving percutaneous drainage (median 6.4 vs. 3.6 cm). Given these clinically important differences in baseline characteristics, we evaluated only short-term outcomes that had multivariable analyses which adjusted for these and other factors. For long-term outcomes from Lambrichts 2019, we calculated unadjusted between-arm effect sizes under the assumption that long-term outcomes would not be confounded by differences in severity of the index episode of acute diverticulitis.

Mali 2019, which was funded by non-industry sources, studied 36 adults with acute diverticular abscesses of at least 4 cm. Eighteen patients who had received percutaneous drainage were compared with 18 matched patients with similar abscess size (±0.5 cm) who had not received percutaneous drainage. Patients were on average in their 60s. Approximately two-thirds of patients (56\% of patients receiving drainage and 67\% not receiving it) were undergoing their first episode of diverticulitis. Demographic, inflammatory, and radiologic factors were similar between the two arms. Because the patients were matched, we considered patients to be adequately similar at baseline and calculated unadjusted effect sizes for all reported outcomes from this NRCS.

We assessed both NRCSs to be at low risk of confounding bias because they used adequate methods to account for potential confounding (see Appendix C). Neither study blinded participants, providers, or outcome assessors; however, the impact of this is likely to be minimal because all outcomes were objective outcomes. We did not detect any issues with other potential biases.

Table 9 summarizes the included results.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, Year, PMID</th>
<th>Time</th>
<th>Intervention</th>
<th>n/N (%)</th>
<th>Effect Size (95% CI)</th>
<th>Reported P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulitis-related mortality, short-term</td>
<td>Mali, 2019, 31320921</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>1/18 (5.6)</td>
<td>OR 1.00 (0.06, 17.33)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>1/18 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality, long-term</td>
<td>Lambrichts, 2019, 30811050</td>
<td>6 yr</td>
<td>Percutaneous drainage</td>
<td>12/115 (10.4)</td>
<td>Unadj OR 2.30 (1.05, 5.02)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No drainage</td>
<td>16/332 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection, short-term</td>
<td>Lambrichts, 2019, 30811050</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>16/115 (13.9)</td>
<td>Adj OR 1.29 (0.56, 2.99)</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No drainage</td>
<td>24/332 (7.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mali, 2019, 31320921</td>
<td>During initial admission</td>
<td>Percutaneous drainage</td>
<td>5/18 (27.8)</td>
<td>OR 1.00 (0.23, 4.30)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>5/18 (27.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection, long-term</td>
<td>Lambrichts, 2019, 30811050</td>
<td>6 yr</td>
<td>Percutaneous drainage</td>
<td>37/115 (32.2)</td>
<td>Adj OR 1.08 (0.69, 1.69)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No drainage</td>
<td>8/7/332 (26.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mali, 2019, 31320921</td>
<td>71 mo</td>
<td>Percutaneous drainage</td>
<td>9/12 (75.0)</td>
<td>OR 1.50 (0.25, 8.84)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>8/12 (66.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stoma</td>
<td>Mali, 2019, 31320921</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>2/12 (16.7)</td>
<td>OR 0.60 (0.08, 4.45)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>3/12 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure (Death or need for surgery)</td>
<td>Lambrichts, 2019, 30811050</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>41/115 (35.7)</td>
<td>Adj OR 1.47 (0.81, 2.68)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No drainage</td>
<td>79/332 (23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mali, 2019, 31320921</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>6/18 (33.3)</td>
<td>OR 0.63 (0.16, 2.41)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>8/18 (44.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readmission, short-term</td>
<td>Mali, 2019, 31320921</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>2/18 (11.1)</td>
<td>OR 0.63 (0.09, 4.28)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>3/18 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>Mali, 2019, 31320921</td>
<td>30 d</td>
<td>Percutaneous drainage</td>
<td>6 d (3, 12)(\text{CC})</td>
<td>Median Difference = 0</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>6 d (3, 10)(\text{DD})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence of diverticulitis, Any, long-term</td>
<td>Lambrichts, 2019, 30811050</td>
<td>6 yr</td>
<td>Percutaneous drainage</td>
<td>29/115 (25.2)</td>
<td>Unadj OR 0.87 (0.53, 1.41)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No drainage</td>
<td>93/332 (28.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mali, 2019, 31320921</td>
<td>71 mo</td>
<td>Percutaneous drainage</td>
<td>1/12 (8.3)</td>
<td>OR 0.45 (0.04, 5.81)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>2/12 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence of diverticulitis, Complicated, long-term</td>
<td>Mali, 2019, 31320921</td>
<td>71 mo</td>
<td>Percutaneous drainage</td>
<td>1/12 (8.3)</td>
<td>OR 1.00 (0.06, 18.09)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antibiotics</td>
<td>1/12 (8.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Adj = adjusted, CI = confidence interval, d = days, IQR = interquartile range, mo = months, NR = not reported, OR = odds ratio, PMID = PubMed identifier, Unadj = unadjusted (analysis of unmatched nonrandomized comparative study), yr = years.

\(\text{CC}\): Median (interquartile range)

\(\text{DD}\): Median (interquartile range)
**Mortality**

Mali 2019 reported that an equal number of patients in each arm (1 of 18) had diverticulitis-related mortality at 30 days (OR 1.00, 95% CI 0.06 to 17.3).

Lambrichts 2019 reported that patients receiving percutaneous drainage had higher all-cause mortality at 6 years (unadjusted OR 2.30, 95% CI 1.05 to 5.02).

**Surgery for Diverticulitis**

Both studies reported on the need for surgery for diverticulitis, specifically sigmoid resection. But both analyses were imprecise or near-imprecise for this outcome, due to insufficient power.

Lambrichts 2019 found no evidence that percutaneous drainage was associated with a reduction in need for sigmoid resection at 30 days, at which point the comparison was imprecise (adjusted OR 1.29, 95% CI 0.56 to 2.99) or at 6 years (adjusted OR 1.08, 95% CI 0.69 to 1.69).

Mali 2019 reported that an equal number of patients in each arm (5 of 18) needed sigmoid resection during initial admission, although the comparison was imprecise (OR 1.00, 95% CI 0.23 to 4.30). The comparison of sigmoid resection rates at 71 months was imprecise (OR 1.50, 95% CI 0.25 to 8.84).

**Stoma**

Mali 2019 reported on stoma rates, but the comparison was imprecise (OR 0.60, 95% CI 0.08 to 4.45).

**Treatment Failure**

Both NRCSs reported on failure of percutaneous drainage, however each defined failure differently.

Lambrichts 2019 defined treatment failure as complications related to acute complicated diverticulitis, such as perforation, obstruction, and fistula. The estimate of relative failure rates between the percutaneous drainage and no percutaneous drainage arms at 30 days was imprecise (adjusted OR 1.47, 95% CI 0.81 to 2.68).

Mali 2019 defined treatment failure as death or need for surgery. The comparison of failure rates between the percutaneous drainage and no percutaneous drainage arms at 30 days was imprecise (OR 0.63, 95% CI 0.16 to 2.41).

**Hospitalization for Diverticulitis**

Mali 2019 found an imprecise association between percutaneous drainage and need for rehospitalization at 30 days (OR 0.63, 95% CI 0.09 to 4.28). The median length of hospital stay was the same (6 days) in patients who had received percutaneous drainage and those who had not.

**Recurrence of Diverticulitis**

Both NRCSs reported on the outcome of recurrence of diverticulitis.

Lambrichts reported that recurrence rates were similar between the percutaneous drainage and no percutaneous drainage arms at 6 years of follow-up (unadjusted OR 0.87, 95% CI 0.53 to 1.41).

In Mali 2019, the between-group comparisons of recurrence of diverticulitis were imprecise, both for recurrence of any diverticulitis (OR 0.45, 95% CI 0.04 to 5.81) and specifically of complicated diverticulitis (OR 1.00, 95% CI 0.06 to 18.1).
Adverse Events
Neither NRCS reported on any adverse events that were attributable to percutaneous drainage. Mali 2019, though, reported on stoma rates, between-group comparisons of which were imprecise. Comparing percutaneous drainage with no drainage, the OR was 0.60 (95% CI 0.08 to 4.45).

Summary of Evidence Pertaining to Interventional Radiology
The evidence profile (Table 10) summarizes the findings. Overall evidence was insufficient to make conclusions.
Two NRCSs, one small with matching (36 participants) and one large with some adjusted and some unadjusted estimates (447 participants), compared patients who underwent percutaneous drainage with those who did not. Estimates were imprecise and, generally sparse, for comparisons of diverticulitis-related mortality, acute sigmoid resection, stoma rates, and short-term rehospitalization for diverticulitis or complications. Based primarily on a single study, no differences in outcomes were found with use of percutaneous drainage for treatment failure at 30 days, length of hospital stay, or long-term recurrence of diverticulitis. Neither study reported on procedure-specific adverse events.
Table 10. Evidence profile for interventional radiology

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Strength of Evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulitis-related mortality, within 30 days</td>
<td>1 (36)</td>
<td>Low</td>
<td>Not applicable</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Sigmoid resection at 30 days</td>
<td>2 (483)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure. Rare event.</td>
</tr>
<tr>
<td>Stoma</td>
<td>1 (24)</td>
<td>Low</td>
<td>Not applicable</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Treatment failure at 30 days</td>
<td>2 (483)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Rehospitalization for diverticulitis or complications</td>
<td>1 (36)</td>
<td>Low</td>
<td>Not applicable</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1 (36)</td>
<td>Low</td>
<td>Not applicable</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Recurrence of diverticulitis</td>
<td>2 (483)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding interventional radiology vs. no procedure</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence</td>
</tr>
</tbody>
</table>

EE One study highly imprecise. Therefore, the conclusion is based on only one study.
FF One study highly imprecise. Therefore, the conclusion is based on only one study.
Key Question 3. Colonoscopy After Acute Diverticulitis

Key points

- There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis may, ultimately, have similar rates of colorectal cancer (CRC) than those who do not undergo colonoscopy; however, no studies evaluated comparative risks of CRC death.

- Among people undergoing colonoscopy, those with a recent diagnosis of acute diverticulitis may be more likely to have colorectal cancer (CRC) than healthy controls (low SoE). It remains unclear whether or not people with recent acute diverticulitis are more likely to be found to have colonic premalignant lesions (insufficient).

- After an episode of acute diverticulitis, about 0.5% to 0.8% die of CRC within approximately 4 years (low SoE).

- Colonoscopy after acute diverticulitis finds that about 2% of people have CRC (moderate SoE), 7% have advanced colonic neoplasia (CRC or advanced adenoma; moderate SoE), 3% have advanced adenoma (large, villous, or high-grade; high SoE), 1.5% have adenomas with high-grade dysplasia (moderate SoE), and 2.4% have large adenomas (≥10 mm; high SoE).

- Patients with recent acute diverticulitis who are age 50 years or older are at about 3-times increased risk of CRC than younger patients (moderate SoE), about 8-times increased risk of advanced colonic neoplasia (high SoE), and possibly at increased risk of advanced adenoma (low SoE).

- Patients with recent complicated acute diverticulitis are at almost 6-times increased risk of CRC than those with recent uncomplicated diverticulitis (high SoE), about 3-times increased risk of advanced colonic neoplasia (high SoE), and probably 2-times increased risk of advanced adenoma (moderate SoE).

- Colonoscopies performed from approximately 6 weeks up to 1 year after acute diverticulitis are incomplete (or fail) in approximately 3.5% of patients (high SoE). No complications associated with colonoscopy were reported among 878 patients, implying a risk of complications of ≤0.9% (high SoE).

Findings Pertaining to Colonoscopy

Overall, 17 studies addressed use of colonoscopy after episodes of acute diverticulitis for the purpose of assessing risk of colorectal cancer (CRC). Three of these compared colonoscopy to no colonoscopy in patients with recent diverticulitis, nine to ten; three compared colonoscopy in patients with recent diverticulitis to healthy controls, one to four; one compared early (in-hospital) colonoscopy to later colonoscopy, five and ten; and ten were single-group studies of patients who underwent colonoscopy. Appendix C Tables C-3-1 to C-3-4 give descriptions of the studies; results are in Appendix D Tables D-3-1 to D-3-7. An additional study of interest that did not meet eligibility criteria is also discussed together with the comparative studies.

Colonoscopy Versus No Colonoscopy

Three NRCS, all retrospective, nine to ten, evaluated colonoscopy compared to no colonoscopy in patients with recent acute diverticulitis. All study participants had recent acute colonic
diverticulitis confirmed by CT. None of the studies reported on family history of CRC. Across studies, participants who underwent colonoscopy were on average in their 50s and about half were men. The studies are at high risk of bias since they did not adjust for differences between groups. None of the studies reported funding sources.

Lau 2011 included 1088 patients with acute left-sided diverticulitis or complicated diverticulitis.99 The total number of participants with complicated diverticulitis was not reported, but 7.5 percent had abscesses, 6.9 percent had local perforations, and 2.0 percent had fistulas. No data were reported on prior history of diverticulitis. The study also did not have access to, and thus did not report, participants’ treatment or surgical histories.

Sallinen 2014 included 536 patients with clinically and CT-diagnosed acute colonic diverticulitis that was treated conservatively, either first attack (75%) or recurrent (25%).100 The percentage of participants with complicated diverticulitis was not reported, but 24 percent had an abscess, and 0.3 percent had a fistula.

In contrast to the other two studies, Soh 2018 included 227 patients presenting with their first episode of CT-proven acute diverticulitis without complications who were managed conservatively.101

The three studies used different comparators as the no colonoscopy arm. Lau 2011 used data from the Western Australian Cancer Registry (within 1 year of CT scan) for whom colonoscopy reports were not available after an episode of acute diverticulitis. It is unclear whether all these patients indeed did not have colonoscopy. Sallinen 2014 included patients followed after treatment of acute diverticulitis who did not undergo colonoscopy for various reasons (e.g., prior colonoscopy within 2 years, patients declined, patients too old). CRC data were obtained from hospital medical records and the Finnish Cancer Registry at least 2 years after the episode of diverticulitis. Soh 2018 included patients who were recommended to have colonoscopy after their diverticulitis who did not undergo followup colonic evaluation. Diagnoses of CRC were sought in national electronic health records at an unreported time point.

In Lau 2011, colonoscopy was conducted within 1 year of diagnostic CT scan. In Sallinen 2014, colonoscopy was performed on average 4 months after hospital discharge. In Soh 2018, colonoscopy was recommended for 6 to 8 weeks after hospital discharge; median interval period was 9 weeks.

The sample sizes varied from 135 to 394 for patients who underwent colonoscopy and 92 to 769 for patients who did not undergo colonoscopy.

**Colorectal cancer death**

None of the comparative studies reported on rates of CRC death.

**Colorectal cancer**

All three studies reported on CRC findings (Figure 5). Under the assumption that the three studies were sufficiently similar to each other, the summary unadjusted OR for CRC was 1.54 (95% CI 0.73 to 3.27; \( I^2 =0\%)\), suggesting no evidence of a difference in rates of CRC ultimately diagnosed among those who did or did not have interval colonoscopy. All of the studies were imprecise (or nearly imprecise) regarding the difference in CRC rates between those who underwent colonoscopy after an episode of acute diverticulitis and comparator groups of people with a history of diverticulitis who did not undergo colonoscopy. ORs ranged from 0.68 to 7.02 across studies. Any suggestion that those who underwent colonoscopy may be at increased risk for having CRC is likely due to underlying biases regarding who completed their colonoscopy.
(e.g., possibly people with a family history of CRC or more complicated diverticulitis are more
likely to have colonoscopy).

**Figure 5. Meta-analysis of colonoscopy versus no colonoscopy: Colorectal
cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>C’scopy</th>
<th>No C’scopy</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 2011</td>
<td>9/319</td>
<td>14/69</td>
<td>1.57 (0.67, 3.65)</td>
</tr>
<tr>
<td>Sallinen 2014</td>
<td>9/394</td>
<td>0/142</td>
<td>7.02 (0.41, 121.5)</td>
</tr>
<tr>
<td>Soh 2018</td>
<td>2/135</td>
<td>2/92</td>
<td>0.68 (0.09, 4.89)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>10' = 0%, P $$\text{Het}$$ = 0.42</strong></td>
<td><strong>1.54 (0.73, 3.26)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, C’scopy = colonoscopy, I² = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, $$\text{P}_{\text{Het}}$$ = statistical heterogeneity P value.

An additional study evaluated the broader question of the association between colonoscopy and CRC in patients with a history of acute diverticulitis. Mortensen 2017 queried the Danish national registry for all long-term residents who had been hospitalized with a primary diagnosis of symptomatic diverticulitis (as adults) over an 18-year period (N=38,773). The primary purpose of this study was to compare rates of CRC (up to 18 years after diverticulitis or colonoscopy) among people with and without a history of diverticulitis (and with and without a colonoscopy). The study did not restrict its analysis to colonoscopies done soon after an episode of diverticulitis nor did they report the relative timeframes of episodes of diverticulitis and colonoscopy (thus, the study did not meet eligibility criteria). This study also did not evaluate lesions found at colonoscopy. Furthermore, the primary analyses included people whose CRC diagnoses occurred before or simultaneous to their diverticulitis-related hospitalization; although, we focus on subgroup analyses excluding these patients. In this subgroup, there were 39,911 adults with a history of hospitalization for diverticulitis. The study did not exclude people who had a colectomy.

In Mortensen 2017, 2.4 percent of people (542/22,646) with a history of diverticulitis who had a colonoscopy (at any time before or after diverticulitis) were diagnosed with CRC (at any time up to 18 years after their diverticulitis episode). Among those who never had a colonoscopy, 3.5 percent (596/17,265) were at some point diagnosed with CRC. The unadjusted risk ratio (RR) was 0.69 (95% CI 0.62 to 0.78); an adjusted RR was not reported.

**Colonoscopy After Diverticulitis Versus Healthy Controls**

Three NRCS, all retrospective, evaluated colonoscopy among patients with diverticulitis and compared findings with matched healthy controls who also underwent colonoscopy. Across studies, the majority of patients had uncomplicated diverticulitis (86% to 92%). Age and sex were generally comparable between two arms within each study. The mean ages of participants ranged from 47 to 61 years old, and males accounted for 41 to 60 percent of the participants. Choi 2014 and Daniels 2015 adjusted only their analysis of advanced adenomas. Lecleire 2014 reported only unadjusted analyses. Choi 2014 did not report funding source; the other two studies were explicitly not funded by industry.
Daniels 2015 compared cohort of patients from two trials who underwent colonoscopy, patients with uncomplicated acute diverticulitis patients (from the DIABOLO trial) and a primary colonoscopy screening population (from the COCOS trial). The DIABOLO trial included adults with first episode of CT-proven left-sided acute diverticulitis. The majority of the participants (93%) had modified Hinchey 1a (pericolic inflammation or phlegmon, per Wasvary) and 7.5% had modified Hinchey 1b (pericolic abscess) diverticulitis; 9.5% had a family history of CRC. Participants from the COCOS trial includes individuals from the general population (aged 50 to 75 years) invited for primary colonoscopy screening. No data on their diverticulitis status/history were reported, but 15.3 percent had a family history of CRC. All patients had left-sided diverticulitis.

Choi 2014 compared patients who underwent colonoscopy within 1 year of acute diverticulitis to age- and sex-matched controls identified from healthy individuals who underwent screening colonoscopy. About 14 percent of the diverticulitis patients had complicated disease and 2.6 percent had a family history of CRC. Of note, the patients with diverticulitis who did not undergo colonoscopy were less likely to have had complicated disease (8.2%, \(P=0.051\)) than patients who did; a similar percentage of them had a family history of CRC (3.1%). No CRC-related data are reported for the group who did not undergo colonoscopy.

Leclaire 2014 matched patients who underwent colonoscopy within 6 months following an episode of acute diverticulitis with sex- and age-matched healthy controls with a family history of CRC or colorectal adenoma (after age 50 years) who also had undergone colonoscopy. The majority (90%) of diverticulitis patients had uncomplicated disease.

**Colorectal cancer death**

None of the comparative studies reported on rates of CRC death.

**Colorectal cancer**

All three studies reported on CRC findings (Figure 6), but reported only unadjusted results for CRC. Under the assumption that the three studies were sufficiently similar to each other, the summary unadjusted OR for CRC was 3.35 (95% CI 0.84 to 13.4), with some heterogeneity among studies (\(I^2=53\%), overall suggesting possible evidence of a difference in CRC rates among adults with a recent history of diverticulitis and the general population. However, a large difference in CRC rates cannot be excluded. Only Choi 2014 reported a statistically significant higher rate of CRC among patients with diverticulitis than the general population matched controls (7.4% vs. 0.7%).

Daniels found no significant difference in left-sided (vs. right-sided) CRC lesions compared with study participants without diverticulitis (5/5 vs. 7/9; \(P=0.51\)). All patients had left-sided diverticulitis.
Mortensen 2017, the Danish national registry study described above, also compared people with a history of diverticulitis-related hospitalizations to matched controls without a history of diverticular disease (including diverticulosis). The primary study matched each adult with diverticulitis to 10 controls. However, in their subgroup analysis excluding those with a history of CRC prior to or simultaneous with the diverticulitis episode, it is unclear who they included among general population controls (although the discrepancy was only 1.4% “too many” control patients). Of note, adults in the general population who had a colonoscopy were at markedly increased risk of CRC compared with those who did not have a colonoscopy (RR = 4.57, 95% CI 4.38 to 4.76; 7.6% [3087/40,777] vs. 1.7% [6040/364,183]). Based on reported numbers, we calculated that the OR comparing those people with a history of diverticulitis (without prior or simultaneous CRC) who had a colonoscopy at any timepoint with (an apparently high-risk population of) adults without a history of diverticulitis who also had a colonoscopy was 0.30 (95% CI 0.27 to 0.33).

High-risk colonic premalignant lesions

All three NRCSs reported high-risk colonic premalignant lesions, but findings were inconsistent.

Daniels 2015 found lower rates of various high-risk lesions than in the general population, opposite in direction to their (statistically nonsignificant) findings about relative of CRC. The crude (unadjusted) ORs for serrated polyps, large adenomas (≥10 mm), adenomas with high-grade dysplasia, advanced adenomas, and advanced colonic neoplasias (CRC or advanced adenoma) were between 0.14 and 0.34, all highly statistically significant. However, the authors note that the statistically significant difference in rates of advanced adenomas (P=0.036) became just nonsignificant after adjustment for age, family history of CRC, smoking, BMI, and cecal intubation (P=0.052); although, no adjusted effect size was reported. Daniels found no significant difference in left-sided (vs. right-sided) advanced colonic neoplasia lesions compared with study participants without diverticulitis (77.4% [24/31] vs. 71.5% [123/172]; P=0.50).

Similarly, Lecleire 2014 found lower risks of premalignant lesions among those with recent diverticulitis. The unadjusted ORs for large adenomas (≥10 mm) and advanced adenomas were similar (advanced adenoma 0.39, 95% CI 0.19 to 0.80; large adenoma 0.38, 95% CI 0.17 to 0.83). The OR for adenomas with high-grade dysplasias was similar, but near imprecise (OR 0.33, 95% CI 0.07 to 164).
In contrast, Choi 2014 reported higher rates of advanced adenoma in the diverticulitis group than the general population (OR 5.14, 95% CI 0.99 to 26.8) and of advanced colonic neoplasia (OR 8.84, 2.90 to 2.70). These findings were consistent with the higher rates of CRC also found.

**Rates of Colorectal Cancer and Abnormal Lesions on Colonoscopy**

We identified 10 single group studies, all retrospective, that evaluated colonoscopy outcomes. The 10 studies were each conducted at a single center and all patients received follow-up colonoscopy after treatment of acute diverticulitis treatment. The mean age of participants across studies ranged from 55 to 64 years old. The sample size varied from 216 to 645 across studies. Among six studies that reported data, the majority of the participants had uncomplicated diverticulitis (ranging from 70 to 82 percent). Although these studies were conducted in 7 different countries, they were similar in terms of participants’ age, sex, and the course of diverticulitis.

For the evaluation of rates of CRC and abnormal lesions, we combined the 10 single group studies with the similar groups in the six comparative studies described above. In addition, a study that compared early (in-hospital) versus “late” (at 6 weeks) colonoscopy was also included here. This latter study is described further in the section on feasibility, below. Therefore, a total of 17 studies were included in the meta-analysis to determine an overall level of CRC and high-risk colonic premalignant lesions following colonoscopy.

The studies were at generally low risk of bias with regards to reporting rates of colonoscopy findings, with clear descriptions of eligibility criteria and outcomes, and no evidence of selection bias (except in regards to which patients were willing to undergo colonoscopy). Two studies were explicitly not funded by industry (Lecleire 2014 and Daniels 2015); the rest did not report funding source.

Figure 7 summarizes the lesions for which meta-analysis was conducted (i.e., all outcomes except CRC death and serrated polyps). The lesion-specific figures are included in Appendix D.
Figure 7. Summary meta-analysis estimates of colonic lesions found on colonoscopy

<table>
<thead>
<tr>
<th>Lesion</th>
<th>CRC</th>
<th>ACN</th>
<th>AA</th>
<th>HGD</th>
<th>≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA est (95% CI)</td>
<td>2.1% (1.4, 3.0)</td>
<td>7.2% (4.9, 10.0)</td>
<td>3.3% (2.3, 4.4)</td>
<td>1.5% (0.2, 3.6)</td>
<td>2.4% (1.6, 3.4)</td>
</tr>
<tr>
<td>[Range]</td>
<td>[0.7-6.7%]</td>
<td>[5.6-7.4%]</td>
<td>[1.5-5.2%]</td>
<td>[0.6-6.6%]</td>
<td>[2.2-2.8%]</td>
</tr>
<tr>
<td>No. studies (Total N)</td>
<td>17 (5306)</td>
<td>3 (766)</td>
<td>6 (1675)</td>
<td>6 (2215)</td>
<td>4 (1210)</td>
</tr>
<tr>
<td>I²</td>
<td>72%</td>
<td>42%</td>
<td>13%</td>
<td>90%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Summary estimates (by meta-analysis) and range of estimates across studies for each lesion. The diamond and vertical line indicate the summary estimate and 95% CI across studies. The size of the diamond is scaled to the total number of individuals across studies. The grey boxes indicate the range of estimates across studies.

Abbreviations: ≥10 mm = large adenomas (≥10 mm), AA = advanced adenoma, ACN = advanced colonic neoplasia, CI = confidence interval, CRC = colorectal cancer, HGD = (adenoma with) high-grade dysplasia, I² = estimate of the statistical heterogeneity across studies (which ranges from 0-100%, where higher values indicate greater heterogeneity across studies), MA est = meta-analysis (summary) estimate.

Colorectal cancer death

Two studies reported on CRC death.108, 112 Among 402 patients who underwent colonoscopy, Elmi 2013 reported 2 CRC deaths among 402 people undergoing colonoscopy (0.5%, 95% CI 0.1 to 2.0) at 2 to 4 years of followup. Among 645 patients who underwent colonoscopy, Ramphal 2018 reported 5 CRC deaths (0.8%, 95% CI 0.3 to 1.8) with the median 39 month followup.

Colorectal cancer

A total of 17 studies reported on rates of CRC following colonoscopy (Figure 7 and Appendix Figure D-KQ3-1). The 17 studies were conducted in 11 countries, including Australia, Canada, Finland, France, Israel, the Netherlands, Portugal, Singapore, South Korea, Spain, and the U.S (these are noted in Appendix Figure D-KQ3-1). Each of these countries has different underlying rates of CRC. Only two eligible studies were conducted in North America.107, 108 Of note, studies generally excluded participants with recent (pre-diverticulitis) colonoscopies.
Across studies, the summary estimate was that 2.1 percent (95% CI 1.4 to 3.0) of people had CRC found on colonoscopy after an episode of acute diverticulitis. The estimates ranged from 0 to 7.6 percent across studies with no clear explanation for the heterogeneity ($I^2 = 72\%$) (e.g., based on participant age, sex, family history of CRC, or severity of diverticulitis). There was no clear pattern by country (or continent); for example, the two studies with the lowest and highest rates of CRC were both conducted in Israel. The one study conducted in the U.S. (Elmi 2013) had an estimate of CRC rate very close to the meta-analyzed summary estimate: 2.2 percent (95% CI 1.0 to 4.2).

Although Choi 2014 (7.4%) and Khoury 2019 (7.6%) did not clearly include different participants than the other studies, excluding these two “outliers,” as expect, reduced the summary estimate somewhat to 1.8 percent (95% CI 1.2 to 2.4), but still with unexplained heterogeneity ($I^2 = 54\%$).

Of note, Mortensen 2017,116 the Danish national registry study described above, reported that of the 1051 people who were diagnosed with CRC after their episode of diverticulitis hospitalization, 626 (59.6%) were diagnosed within 500 days. This translates to 1.6 percent of the people hospitalized for diverticulitis who did not have a prior or simultaneous diagnosis of CRC. There was no indication of when (or if) colonoscopies were conducted for those diagnosed with CRC.

**Advanced colonic neoplasia**

Three studies reported on rates of advanced colonic neoplasia, defined as either CRC or advanced adenoma (Figure 7 and Appendix Figure D-KQ3-2).102, 103, 114 Across studies, the summary estimate was that 7.2 percent (95% CI 4.9 to 10.0) of people had advanced colonic neoplasia found on colonoscopy after an episode of acute diverticulitis. However, the studies were somewhat heterogeneous ($I^2 = 42\%$) with estimates ranging from 5.6 to 10.7 percent. We found no clear explanation for the heterogeneity.

**High-risk colonic premalignant lesions**

Here we describe each high-risk colonic lesion individually, although it is important to note that these lesions are not mutually exclusive. An individual may have separate lesions of different types and individual lesions may be classified as one of several, or perhaps as multiple, lesion types. Furthermore, most studies reported only specific lesions (either due to varying definitions of the lesions or due to omissions). Thus, the summary estimates of frequencies of lesions cannot be simply summed across lesions.

**Advanced Adenoma**

Seven studies reported on rates of advanced adenoma (Figure 7 and Appendix Figure D-KQ3-3).101, 102, 104, 106, 107, 114, 115 Most studies defined advanced adenomas as either large (≥10 mm), villous, or of high grade. Lecleire 2014 also included invasive cancer, but for our analysis, we have excluded the one patient with CRC. Brar 2013 also included serrated adenomas and is thus excluded from the meta-analysis. Suhardja 2017 did not define.

Across the six studies (excluding Brar 2013), the summary estimate was that 3.3 percent (95% CI 2.3 to 4.4) of people had advanced adenomas found on colonoscopy after an episode of acute diverticulitis. The study-level estimates ranged from 1.5 to 5.2 percent, with minor statistical heterogeneity across studies.

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**GG** Based on Figure 2 in the article, subtracting out the 87 simultaneous diagnoses of diverticulitis and CRC.
Brar 2013 found that 9.2 percent (95% CI 5.9 to 13.5) had advanced adenomas, which included serrated polyps by their definition.

**Adenomas with High-Grade Dysplasia**

Six studies reported on rates of adenomas with “high-grade dysplasia” (Figure 7 and Appendix Figure D-KQ3-4). This term may be variably defined and implicitly or explicitly included various other lesions.

Across studies, the summary estimate was that 1.5 percent (95% CI 0.2 to 3.6) of people had adenomas with high-grade dysplasia found on colonoscopy after an episode of acute diverticulitis. Four of the six studies had estimates that ranged from 0 to 1.0 percent, but two studies had much higher estimates, at 3.0 and 6.6 percent. The heterogeneity (I² = 90%) may be due to differing definitions of high-grade dysplasia, although the studies generally did not define the outcome. Excluding the two “high estimate” studies yields a summary estimate of 0.5 percent (95% CI 0.1 to 1.2; I² = 47%). Excluding just the highest estimate (Meireles 2015) yields a summary estimate of 0.8 percent (95% CI 0.2 to 1.9; I² = 71%). Although, these alternative scenarios are presented, it should be noted that there is no intrinsic reason to think that the excluded studies are “less correct” than the remaining.

**Adenoma ≥10 mm**

Four studies reported on rates of adenoma ≥10 mm (Figure 7 and Appendix Figure D-KQ3-5). Across studies, the summary estimate was that 2.4 percent (95% CI 1.6 to 3.4) of people had large adenomas found on colonoscopy after an episode of acute diverticulitis. The estimates were all very similar, with no heterogeneity.

**Serrated polyp**

Two studies reported on rates of serrated polyps. The two reported very different rates of serrated polyps, possibly due to differing definitions. Daniels 2015 reported a high rate (54/401; 13.2%, 95% CI 10.1 to 16.9) from the Dutch DIABOLO study. Seoane Urgorri 2018 reported a low rate (2/216; 0.9%, 95% CI 0.1 to 3.3) in a Spanish sample of patients.

**Subgroup Analyses**

Ten studies compared rates of CRC and other dysplasias among subgroups of participants. Of primary interest were comparisons by age and recent complicated (vs. uncomplicated) diverticulitis. Other comparisons included sex, right versus left sided diverticulitis, and others. As described below, only three studies conducted multivariable analyses. The other studies are at high risk of bias due to potentially unadjusted differences between compared subgroups. None of the studies reported funding source.

Figure 8 summarizes the comparisons between subgroups for which meta-analysis was conducted. The comparison-specific figures are included in Appendix D.
Figure 8. Summary meta-analysis estimates of subgroup analyses

<table>
<thead>
<tr>
<th>Subgroup comparison</th>
<th>No. Studies (N Total)</th>
<th>Lesion</th>
<th>OR (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 yo vs &lt;50 yo</td>
<td>4 (1119)</td>
<td>CRC</td>
<td>Older more likely 3.31 (1.58, 6.95) *</td>
<td>43%</td>
</tr>
<tr>
<td>Complicated vs. uncomplicated</td>
<td>7 (1965)</td>
<td>Advanced colonic neoplasia</td>
<td>Complicated more likely 5.72 (7.73, 12.0)</td>
<td>21%</td>
</tr>
<tr>
<td>Complicated vs. uncomplicated</td>
<td>4 (886)</td>
<td>Advanced Adenoma</td>
<td>Complicated more likely 3.44 (1.21, 13.1)</td>
<td>0%</td>
</tr>
<tr>
<td>Complicated vs. uncomplicated</td>
<td>4 (887)</td>
<td></td>
<td>Complicated more likely 1.95 (0.91, 4.17)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Summary estimates (by meta-analysis) for each subgroup analysis. Each diamond indicates the summary estimate and 95% CI across studies.

* Peto odds ratio

Abbreviations: CI = confidence interval, I² = estimate of the statistical heterogeneity across studies (which ranges from 0-100%, where higher values indicate greater heterogeneity across studies), OR = odds ratio, yo = years old.

**Age (≥50 Versus <50 Years)**

Five studies compared patients older than versus at least 50 years of age. Notably, this is the age threshold that the USPSTF, ACP, and the U.S. Multi-Society Task Force of Colorectal Cancer (which includes the AGA) recommend screening for CRC in all adults (although the USPSTF recommendations are being updated). As will be described, Brar 2013 also evaluated age as a continuous variable.

**Colorectal Cancer**

Four studies compared the rate of CRC following colonoscopy among patients older and younger than 50 years of age (Figure 8 and Appendix Figure D-KQ3-6). Under the assumption that the four studies were sufficiently similar to each other, the summary Peto OR for CRC was 3.31 (95% CI 1.58 to 6.95), with moderate heterogeneity. Three of the studies found no CRC among patients under age 50. There was no obvious difference between the fourth study, Meireles 2015, which found 4 percent of people age 50 or younger to have CRC and the other three studies.

**Advanced Colonic Neoplasia**

Four studies conducted multivariable analyses and reported statistically significant higher rates of advanced colonic neoplasia (CRC or advanced adenoma) in older patients. Andrade 2016 and Choi 2014 had similar findings with adjusted OR = 8.12 (95% CI 2.46 to 45.1) and 9.13 (95% CI 1.97 to 42.3), respectively that patients of ages 50 years and older were more likely to have advanced colonic neoplasia. Seoane Urgorri 2018 reported that 7.8 percent of patients >50 years old had advanced colonic neoplasias compared with none (0%) for younger people (P = 0.02), but they did not report the numbers of study participants in each age subgroup. Brar 2013 also evaluated age, but as a continuous variable, and found an adjusted OR of 1.04 (95% CI 1.01 to 1.08) for advanced colonic neoplasia per year of age.
**Advanced Adenoma**

Brar 2013 and Choi 2014 each found no significant difference in rates of advanced adenoma by age group, although both trended toward more frequent advanced adenomas in those over age 50 years. Brar 2013 yielded an OR of 3.27 (95% CI 0.93 to 11.5). Choi 2014 yielded an OR of 1.68 (95% CI 0.27 to 10.3).

**Complicated Versus Uncomplicated Diverticulitis**

Seven studies compared patients with and without complicated diverticulitis (or with or without abscess).

**Colorectal Cancer**

All seven studies compared the rate of CRC following colonoscopy between patients with complicated diverticulitis and patients with uncomplicated diverticulitis (Figure 8 and Appendix Figure D-KQ3-7). In contrast with the other studies, Elmi 2013 compared those who had had abscesses to those who did not. Combining all studies (assuming for the purpose of this analysis that in Elmi 2013 everyone with complicated diverticulitis had an abscess), the summary unadjusted OR for CRC was 5.72 (95% CI 2.73 to 12.0), with little heterogeneity across studies ($I^2 = 21\%$). Across studies, ORs ranged from 2.5 to 40.4. Excluding Elmi 2013 resulted in a similar summary estimate (OR = 6.89, 95% CI 2.57 to 18.5, $I^2 = 41\%$).

**Advanced Colonic Neoplasia**

Four studies that compared complicated versus uncomplicated diverticulitis evaluated advanced colonic neoplasia (Figure 8 and Figure D-KQ3-8). As indicated in the figure, three reported multivariable analyses and one of those evaluated abscess versus no abscess. All studies provided similar ORs for relative rate of advanced colonic neoplasia between those with and without complicated diverticulitis. The overall summary OR was 3.44 (95% CI 1.99 to 13.1) suggesting complicated diverticulitis being associated with increased risk of advanced colonic neoplasia on colonoscopy.

**Advanced Adenoma**

Four studies evaluated advanced adenomas (Figure 8 and Figure D-KQ3-9). Each study’s estimate of the association between complicated diverticulitis and risk of advanced adenoma was not statistically significant. Across studies, the summary OR of complicated versus uncomplicated diverticulitis for risk of advanced adenoma was near significant at 1.95 (95% CI 0.91 to 4.17), suggesting possible increased risk among people with complicated diverticulitis.

**Adenomas With High-Grade Dysplasias**

Meireles 2015 reported that 9 of 80 (11%) patients with complicated diverticulitis had adenomas with high-grade dysplasia found on colonoscopy compared with 19 of 347 (5.5%) with uncomplicated diverticulitis. This translated into a near-significant OR of 2.19 (95% CI 0.95 to 5.03).

**Other Subgroup Analyses**

Appendix D Tables D-3-1 to D-3-7 present more results on colonoscopy subgroup analyses.
Left Versus Right Sided Diverticulitis

Two studies from East Asia compared people with right or left sided diverticulitis.\textsuperscript{101, 102} Of note, right-sided diverticulitis is more common in East Asia.

Both reported risks of CRC but provided imprecise estimates. Choi 2014 reported 2 CRC among 23 (8.7\%) patients with left-sided diverticulitis and 9 of 126 (7.1\%) with right-sided (OR = 1.24, 95\% CI 0.25 to 6.13). Soh 2018 reported 2 of 54 (3.7\%) left sided versus 2 of 178 (1.1\%) right sided (OR = 3.38, 95\% CI 0.47 to 24.6).

Choi 2014 also reported comparative rates of advanced colonic neoplasia (OR 1.30, 95\% CI 0.34 to 4.99) and advanced adenoma (OR 1.39, 95\% CI 0.15 to 12.99).

Male Versus Female

Two studies provided imprecise estimates of the relative rates of CRC or advanced colonic neoplasia by sex.\textsuperscript{102, 108} Elmi 2013 found that 1.2\% (2/167) of men and 3.0\% (7/235) of women had CRC (OR 0.39, 95\% CI 0.08 to 1.92). Choi 2014 reported a multivariable analysis that found an adjusted OR of 1.08 (95\% CI 0.35 to 3.34); they did not report event counts by sex.

Alarm symptoms

Ramphal 2018 reported that 9 of 205 (4.4\%) patients with alarm symptoms, but only 1 of 440 (0.2\%) patients without alarm symptoms had CRC.\textsuperscript{112} This translated into an OR of 20.2, 95\% CI 2.54 to 160). Alarm symptoms included unintentional weight loss, a change in bowel habits, bloody stool and/or persistent abdominal pain.

Anemia

In their multivariable analysis, Brar 2013 found no significant association between anemia and risk of advanced colonic neoplasia (adjusted OR 0.78, 95\% CI 0.24 to 2.57).

Previous Attack of Diverticulitis

Brar 2013 also found no significant association between history of prior diverticulitis and risk of advanced colonic neoplasia (OR 2.28, 95\% CI 0.76 to 7.46). The definition of previous attack, however, was not completely clear.

Colonoscopy: Complications, Tolerance, Feasibility, and Completion of Procedure

Four studies explicitly reported no major complications (Meireles 2015 and Seoane Urgorri 2018)\textsuperscript{111, 114} or (overall) no complications (Choi 2014 and Lahat 2007)\textsuperscript{102, 105} related to colonoscopy across 878 patients overall, implying a confidence interval of 0 to 0.9 percent. The other 13 studies did not report on complications associated with colonoscopy.

Three studies reported on rates of failed/incomplete colonoscopy procedure (Figure 9).\textsuperscript{105, 106, 115} Combination of the three cohorts that performed colonoscopy after hospital discharge (within 1 year or at approximately 6 weeks) yielded a summary estimate that 3.5\% (95\% CI 2.1 to 5.3) of patients had a failed or incomplete procedure.

Lahat 2007 was designed to compare in-hospital colonoscopy with later colonoscopy (at only 6 weeks after discharge). The study found a nonsignificantly higher rate of incomplete colonoscopies among those with in-hospital rather than later colonoscopy (17.8\% vs. 7.3\%; \(P = 0.16\)). However, the study also found that only 3/45 (6.7\%) of those with inpatient colonoscopy failed to show (or refused) colonoscopy, as opposed to 10/41 (24.4\%) who did not show for their
6 week colonoscopy (P=0.03). In total 34/45 (75.6%) of in-hospital colonoscopy patients had a completed colonoscopy.

**Figure 9. Meta-analysis of colonoscopy after acute diverticulitis: Percent with failed or incomplete colonoscopy**

<table>
<thead>
<tr>
<th>Study</th>
<th>n/N</th>
<th>Pct (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade 2017 (w/in 1 yr)</td>
<td>9/261</td>
<td>3.4 (1.8, 6.4)</td>
</tr>
<tr>
<td>Suhardja 2017 (w/in 1 yr)</td>
<td>10/270</td>
<td>3.7 (2.0, 6.7)</td>
</tr>
<tr>
<td>Lahal 2007 (6 wk)</td>
<td>3/41</td>
<td>7.3 (2.5, 19.4)</td>
</tr>
<tr>
<td>Overall (P=0%, P_Het = 0.50)</td>
<td></td>
<td>3.5 (2.1, 5.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, I² = measure of statistical heterogeneity (% of heterogeneity not due to random chance), Pct = percent, P_Het = chi-squared P value of statistical heterogeneity (not the P value of the estimate), wk = weeks (after hospitalization).

**Summary of Evidence Pertaining to Colonoscopy**

The evidence profile summarizing results and providing SoE is in Table 11.

Three studies compared groups of patients who had recent episodes of acute diverticulitis who did or did not undergo post-recovery colonoscopy. None addressed the clinically most important outcome of CRC death. Likely because of lack of power (due to the relatively low percentage of people with CRC discovered after acute diverticulitis), overall, with low SoE, the studies do not support that CRC is uncovered more frequently among those receiving colonoscopy soon after diverticulitis (summary OR 1.54, 95% CI 0.73 to 3.26). Any suggestion that those who underwent colonoscopy may be at increased risk for having CRC is likely due to underlying biases regarding who completed their colonoscopy (e.g., possibly people with a family history of CRC or more complicated diverticulitis are more likely to have colonoscopy).

Three studies compared people undergoing colonoscopy with and without recent episodes of acute diverticulitis. Again, none evaluated CRC death. Based on only unadjusted analyses, there is low SoE that those with recent acute diverticulitis may be more likely to have CRC than the general population (OR 3.35, 95% CI 0.84 to 13.4).

Seventeen studies provided variable SoE regarding likelihood of CRC and high-risk colonic lesions among people with recent episodes of acute diverticulitis. In summary, CRC death occurred in about 0.5 to 0.8 percent of patients (2 studies), and colonoscopy revealed CRC in 2.1 percent (95% CI 1.4 to 3.0; 17 studies), advanced colonic neoplasia in 7.2 percent (95% CI 4.9 to 10.0; 3 studies), advanced adenoma in 3.3 percent (95% CI 2.3 to 4.4; 6 studies), adenomas with high-grade dysplasia (which likely includes other specific lesions) in 1.5 percent (95% CI 0.2 to 3.6; 6 studies), and large adenomas in 2.4 percent (95% CI 1.6 to 3.4; 4 studies).

Ten studies evaluated various risk factors for different abnormal colonoscopy findings; most of the analyses were conducted by only a single studies. Among the more commonly reported analyses, patients 50 years or older were probably about three-times as likely to have CRC than younger patients (OR 3.31, 95% CI 1.58 to 6.95; 4 studies; moderate SoE), 8- to 9-times more likely to have advanced colonic neoplasias (3 studies; high SoE), and maybe 1.7- to 3.3-times higher risk of advanced adenomas (2 studies; low SoE). Patients with recent complicated diverticulitis (compared with those with uncomplicated diverticulitis) were about six times more likely to have CRC (OR 5.72, 95% CI 2.73 to 12.0; 7 studies; high SoE), three times more likely
to have advanced colonic neoplasia (OR 3.44, 95% CI 1.99 to 5.94, 4 studies; high SoE), and probably about twice as likely to have advanced adenomas (OR 1.95, 95% CI 0.91 to 4.17; 4 studies; moderate SoE).

Complications due to colonoscopy after acute diverticulitis are rare. Based on six studies that explicitly reported on complications, none (of 878) patients experienced a procedure-related complication (95% CI 0 to 0.9%; high SoE). Failed or incomplete colonoscopies were reported to be uncommon (3.5%, 95% CI 2.1 to 5.3; 3 studies; high SoE). One RCT compared in-hospital colonoscopy to colonoscopy about 6 weeks after discharge finding similar rates of completed colonoscopies between the groups.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>No. Studies</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy vs. no colonoscopy</td>
<td>CRC death</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence</td>
</tr>
<tr>
<td></td>
<td>CRC</td>
<td>3 (1851)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Low</td>
<td>No evidence of a difference OR 1.54 (0.73, 3.26)</td>
</tr>
<tr>
<td>Diverticulitis vs. general population</td>
<td>CRC death</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence</td>
</tr>
<tr>
<td></td>
<td>CRC</td>
<td>3 (954)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Low</td>
<td>Possible increased risk after diverticulitis OR 3.35 (0.84, 13.4)</td>
</tr>
<tr>
<td></td>
<td>Premalignant lesions</td>
<td>3 (954)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient</td>
<td>No conclusion regarding colonoscopy in diverticulitis vs. general population</td>
</tr>
<tr>
<td>Rates of abnormal findings (no comparison)</td>
<td>CRC death</td>
<td>2 (1047)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Low</td>
<td>0.5% or 0.8%</td>
</tr>
<tr>
<td></td>
<td>CRC</td>
<td>17 (5306)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>2.1% (1.4, 3.0)</td>
</tr>
<tr>
<td></td>
<td>ACN</td>
<td>3 (766)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>7.2% (4.9, 10.0)</td>
</tr>
<tr>
<td></td>
<td>Advanced adenoma</td>
<td>6 (1426)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>3.3% (2.3, 4.4)</td>
</tr>
<tr>
<td></td>
<td>High-grade dysplasia</td>
<td>6 (2215)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>1.5% (0.2, 3.6)</td>
</tr>
<tr>
<td></td>
<td>Adenoma ≥10 mm</td>
<td>4 (1210)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>2.4 (1.6, 3.4)</td>
</tr>
<tr>
<td></td>
<td>Serrated polyp</td>
<td>2 (617)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>Estimate unclear</td>
</tr>
<tr>
<td>Age ≥50 vs. &lt;50 y</td>
<td>CRC</td>
<td>4 (1158)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>Older at increased risk OR 3.31 (1.58, 6.95)</td>
</tr>
<tr>
<td></td>
<td>ACN</td>
<td>3 (650)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>Older at increased risk OR ~8 to 9</td>
</tr>
<tr>
<td></td>
<td>Advanced adenoma</td>
<td>2 (398)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Low</td>
<td>Possibly older at increased risk OR 1.7 or 3.3, but imprecise or NS</td>
</tr>
<tr>
<td>Complicated vs. uncomplicated</td>
<td>CRC</td>
<td>7 (1965)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>Hx of complicated at increased risk OR 5.72 (2.73, 12.0)</td>
</tr>
<tr>
<td></td>
<td>ACN</td>
<td>4 (866)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>Hx of complicated at increased risk OR 3.44 (1.99, 5.94)</td>
</tr>
<tr>
<td></td>
<td>Advanced adenoma</td>
<td>3 (671)</td>
<td>Low</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>Hx of complicated maybe at increased risk OR 1.95 (0.91, 4.17)</td>
</tr>
<tr>
<td></td>
<td>High-grade dysplasia</td>
<td>1 (427)</td>
<td>Low</td>
<td>N/A</td>
<td>Precise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding complicated vs. uncomplicated</td>
</tr>
<tr>
<td>Complications (no comparison)</td>
<td>Complications</td>
<td>4 (878)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>0% (0 to 0.9)</td>
</tr>
<tr>
<td>Feasibility (no comparison)</td>
<td>Incomplete colonoscopy</td>
<td>3 (572)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>3.5% (2.1, 5.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ACN = advanced colonic neoplasia, CRC = colorectal cancer, Hx of = history of (recent), NS = not statistically significant, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

* With recent acute diverticulitis
Key Question 4. Interventions to Prevent Recurrence

Key Question 4 a/b. Nonsurgical Interventions

Key points
- In patients with a history of acute diverticulitis, 5-ASA probably does not reduce the risk of recurrence of diverticulitis (moderate SoE) and may increase the risk by a small amount.
- The evidence does not suggest that 5-ASA increases the risk of adverse events compared with placebo treatments (moderate SoE).
- There was insufficient evidence to make conclusions for other outcomes or other interventions due to sparse evidence and underpowered studies. These included rifaximin, combination 5-ASA and rifaximin, probiotics, and burdock tea.
- Notably, no comparative study evaluated medical nutrition therapy.

Findings Pertaining to Nonsurgical Interventions

Twelve studies (10 RCTs, one NRCS, and one single-group study) evaluated nonsurgical (pharmacologic and nonpharmacologic) interventions to prevent recurrent diverticulitis (Appendix C Tables C-4ab-1 to C-4ab-3). The results of the studies are summarized in Appendix D Tables D-4ab-1 to D-4ab-2.

The average age of participants ranged from 48 years to 67 years across studies. Between 31 and 66 percent of study participants were male. All studies included patients who had a documented prior episode of acute diverticulitis; however, two RCTs (the PREVENT-1 and PREVENT-2 trials, published in the same article) included 0.3 and 0.5 percent of patients without prior diverticulitis, respectively. Five RCTs were funded by industry, and one was explicitly not funded by industry; the remaining six studies did not report their funding sources.

Six RCTs compared 5-ASA (mesalamine) to placebo. Other comparisons between interventions were evaluated by single studies only. These included comparisons of probiotics versus placebo, rifaximin versus placebo, combination 5-ASA and probiotics versus placebo, combination 5-ASA and probiotics versus probiotics alone, combination 5-ASA and probiotics versus 5-ASA alone, combination rifaximin and 5-ASA versus rifaximin alone, and 5-ASA versus rifaximin. The only comparative study of nonpharmacologic interventions was one RCT that compared burdock tea to control. Finally, one single-group study reported on harms of 5-ASA. Of note, none of the studies evaluated medical nutrition therapy.

We did not detect any major methodological concerns in six RCTs (the PREVENT-1, PREVENT-2, SAG-37, and SAG-51 trials, Lanas 2013, and Mizuki 2019) (Appendix C Table C-3. The RCT that compared combination rifaximin and 5-ASA with rifaximin alone (Tursi 2002) did not report the random sequence generation method or whether allocation was concealed. Three RCTs (Tursi 2002, Tursi 2007, and Kvasnovsky 2007) did not conduct blinding of participants, care providers, or outcome assessors. One RCT (Stollman 2013) followed only participants who were compliant with 12 weeks of therapy, and thus had a high withdrawal rate. We assessed the NRCS (Festa 2017) at low risk of confounding bias because it reported conducting multivariate Cox regression to account for potential confounding. We assessed Festa 2017 at low risk of bias in selection of participants into the study. We could not adequately
assess the risk of bias in the single-group study (Silva Sanchez 2014) because it has been reported only as a conference abstract.

5-ASA Versus Placebo

Six RCTs (the PREVENT-1 and PREVENT-2 [both in Raskin 2014], SAG-37 and SAG-31 trials [both in Kruis 2017], Parente 2013, and Stollman 2013) compared 5-ASA (a variety of doses) with placebo in a total of 1836 participants, almost all of whom had prior histories of acute diverticulitis.\textsuperscript{121, 123, 125, 126} In addition, one single-group study reported harms in 45 patients receiving 4.8 g/day of 5-ASA.\textsuperscript{127}

Recurrence of Diverticulitis

All six RCTs reported on the outcome of recurrence of diverticulitis. Both the PREVENT-1 and PREVENT-2 trials compared three doses of 5-ASA (1.2, 2.4, and 4.8 g/day) with placebo. SAG-51 compared two doses of 5-ASA (1.5 and 3 g/day) with placebo. Parente 2013, Stollman 2013 [DIVA], and SAG-37 each compared a single dose (1.6, 2.4, and 3 g/day, respectively) with placebo. To allow meta-analysis, we split the number of people in the placebo groups of the multidose studies to avoid double-counting the placebo groups. By meta-analysis, the summary OR for diverticulitis recurrence with 5-ASA was 1.15 (95% CI 0.92 to 1.44), suggesting 5-ASA may increase the risk of recurrence by a small amount (Figure 10). There was no statistical evidence of heterogeneity across studies. Other than different doses of 5-ASA, we did not identify important clinical differences across studies. However, consistent with the lack of statistical heterogeneity across studies, we do not see evidence that effects differ by dose (note that the forest plot is arranged by 5-ASA dose), which may also suggest a lack of effect.

Figure 10. Meta-analysis of 5-ASA versus placebo: Recurrence of diverticulitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose, mg</th>
<th>Months</th>
<th>n/N</th>
<th>5-ASA</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT 1</td>
<td>1.2</td>
<td>24</td>
<td>54/143</td>
<td>17.3/49*</td>
<td></td>
<td>1.11 (0.56, 2.18)</td>
</tr>
<tr>
<td>PREVENT 2</td>
<td>1.2</td>
<td>24</td>
<td>55/148</td>
<td>15.3/47.3*</td>
<td></td>
<td>1.23 (0.62, 2.47)</td>
</tr>
<tr>
<td>SAG-51</td>
<td>1.5</td>
<td>12</td>
<td>15/87</td>
<td>8.5/40.5*</td>
<td></td>
<td>0.78 (0.31, 2.01)</td>
</tr>
<tr>
<td>Parente 2013</td>
<td>1.6</td>
<td>24</td>
<td>6/45</td>
<td>13/47</td>
<td></td>
<td>0.40 (0.14, 1.17)</td>
</tr>
<tr>
<td>DIVA</td>
<td>2.4</td>
<td>9</td>
<td>9/32</td>
<td>9/29</td>
<td></td>
<td>0.87 (0.29, 2.82)</td>
</tr>
<tr>
<td>PREVENT 1</td>
<td>2.4</td>
<td>24</td>
<td>53/143</td>
<td>17.3/49*</td>
<td></td>
<td>1.08 (0.55, 2.12)</td>
</tr>
<tr>
<td>PREVENT 2</td>
<td>2.4</td>
<td>24</td>
<td>60/147</td>
<td>15.3/47.3*</td>
<td></td>
<td>1.44 (0.72, 2.87)</td>
</tr>
<tr>
<td>SAG-37</td>
<td>3</td>
<td>12</td>
<td>31/165</td>
<td>20/168</td>
<td></td>
<td>1.71 (0.93, 3.15)</td>
</tr>
<tr>
<td>SAG-51</td>
<td>3</td>
<td>12</td>
<td>15/75</td>
<td>8.5/40.5*</td>
<td></td>
<td>0.94 (0.37, 2.42)</td>
</tr>
<tr>
<td>PREVENT 1</td>
<td>4.8</td>
<td>24</td>
<td>71/150</td>
<td>17.3/49*</td>
<td></td>
<td>1.64 (0.84, 3.20)</td>
</tr>
<tr>
<td>PREVENT 2</td>
<td>4.8</td>
<td>24</td>
<td>46/149</td>
<td>15.3/47.3*</td>
<td></td>
<td>0.93 (0.46, 1.88)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.15 (0.92, 1.44)</td>
</tr>
</tbody>
</table>

Abbreviations: 5-ASA = 5-aminosalicylic acid, CI = confidence interval, I\textsuperscript{2} = measure of statistical heterogeneity (% of heterogeneity not due to random chance), mg = milligrams, OR = odds ratio, P\textsubscript{HET} = statistical heterogeneity P value.
Three RCTs (Parente 2013, SAG-51, and DIVA [Stollman 2013]) reported on time to recurrence (in days) (Table 12) but had conflicting results. Parente 2013 reported worse outcomes with 5-ASA: that patients receiving 1.6 g/day of 5-ASA (10 d/mo) had a shorter mean time to recurrence than patients receiving placebo (mean difference [MD] −151 days, 95% CI −366 to −66). The other two trials found no statistically significant differences between 5-ASA and placebo (Parente 2013: HR 1.02 for 3 g/d and 0.74 for 1.5 g/d; Stollman 2013: 209 days longer before recurrence with 5-ASA, but reported as NS, implying a very wide confidence interval).

Stollman 2013 reported the numbers of patients who withdrew from the study because of surgery for diverticulitis (Table 13). These included two patients in the 5-ASA group and one in the placebo group, implying an OR = 2.11 (95% CI 0.18 to 24.2).

**Symptom Scores**

Parente 2013 reported on the impact of therapy on physical condition at 24 months using the Therapy Impact Questionnaire (TIQ) (Table 12). Scores on the TIQ range from 0 to 40, with lower scores suggesting a better outcome. At 24 months, patients in the 5-ASA arm had lower mean TIQ scores than patients in the placebo arm (MD −2.9, 95% CI −4.8 to −1.0), suggesting a beneficial effect of 5-ASA. However, we found no information regarding what a minimal clinically important difference would be. Also of note, the study gathered data on the quality of life component of the TIQ but did not report followup data or analyses for this component.

Stollman 2013 reported changes in a Global Symptom Score (GSS), which was developed for the study (see Table 12 footnote). Data were incompletely reported but found that GSS scores were lower (better) with 5-ASA than placebo at all followup timepoints, but mostly nonsignificantly so. The study does not claim any differences were clinically significant. The study also reported numbers of patients who achieved a “GSS response” (score of 0-1 of 6 on all 10 subscales) and a “complete GSS response” (score of 0 on all subscales). At 12 months, the study found no significant difference (implicitly) in GSS response between 5-ASA (67%) and placebo (50%), but a just-significant difference in complete GSS response (41% vs. 18%, P=0.452).
Table 12. Nonsurgical treatments to prevent recurrence: Continuous outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, PMID</th>
<th>Time (mo)</th>
<th>Arm</th>
<th>N</th>
<th>Mean (SD or 95% CI)</th>
<th>Effect Size (95% CI)</th>
<th>Reported P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-ASA vs. placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to recurrence of diverticulitis (days)</td>
<td>SAG-51 2017</td>
<td>12</td>
<td>5-ASA (3.0 g/d)</td>
<td>NR</td>
<td>191 (125)</td>
<td>HR 1.02 (0.53, 1.94)</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-ASA (1.5 g/d)</td>
<td>NR</td>
<td>116 (134)</td>
<td>HR 0.74 (0.38, 1.43)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Parente, 2013, 23754545</td>
<td>24</td>
<td>5-ASA (1.6 g/d), 10 d/mo</td>
<td>45</td>
<td>219 (180)</td>
<td>MD −151 (−236, −66)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>370 (227)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) x 12 wk</td>
<td>25</td>
<td>308.7 (NR)</td>
<td>MD 208.6 (NR)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>28</td>
<td>100.1 (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy Impact Questionnaire (TIQ score)† Physical Condition</td>
<td>Parente, 2013, 23754545</td>
<td>24‡</td>
<td>5-ASA (1.6 g/d), 10 d/mo</td>
<td>45</td>
<td>0: 8.1 (3.8) 24: 5.4 (2.7)</td>
<td>24: MD −2.9 (−4.8, −1.0)‡</td>
<td>MD 0.022†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>0: 8.7 (4.4) 24: 8.3 (5.7)</td>
<td>0-24: NMD −2.3 (−4.1, −0.5)‡</td>
<td></td>
</tr>
<tr>
<td>Global Symptom Score (GSS)‡</td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) x 12 wk</td>
<td>27</td>
<td>0: 22.0 (8.6) 9: 1.0 [median]</td>
<td>12: MD ⩾4.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>29</td>
<td>0: 23.5 (9.1) 9: 5.0 [median]</td>
<td>0-12: NMD ⩾2.5</td>
<td></td>
</tr>
<tr>
<td><strong>(5-ASA + probiotics) vs. placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to recurrence of diverticulitis (days)</td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) + probiotics x 12 wk</td>
<td>27</td>
<td>280.7 (NR)</td>
<td>MD: 180.6 (NR)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>29</td>
<td>100.1 (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Symptom Score (GSS)#</td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) + probiotics x 12 wk</td>
<td>27</td>
<td>0: 19.4 (NR) 12: 4.4 [median]</td>
<td>12: MD ⩾0.6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>29</td>
<td>0: 23.5 (9.1) 12: 5.0 [median]</td>
<td>0-12: NMD ⩾3.5</td>
<td></td>
</tr>
<tr>
<td><strong>Burdock tea vs. no treatment</strong></td>
<td>Mizuki, 2019, 31043657</td>
<td>30</td>
<td>Burdock tea (4.5 g/d)</td>
<td>44</td>
<td>59.3 (54.0, 64.7)</td>
<td>MD 14.2 (4.5, 23.9)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No intervention</td>
<td>44</td>
<td>45.1 (37.1, 53.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 5-ASA = 5-aminosalicylic acid, CI = confidence interval, d = days, HR = hazard ratio, mo = month, MD = mean difference (between groups), NMD = net mean difference (difference-in-difference), NR = not reported, NS = not statistically significant, OR = odds ratio, PMID = PubMed identifier, SD = standard deviation, TIQ = Therapy Impact Questionnaire (0 to 40, lower better), y = years.

* For comparisons between active therapies (e.g., combination 5-ASA plus rifaximin vs. rifaximin), see Appendix Table D-4ab-2.

† Score to measure physical condition. Maximum (worst) score: 40. No information is available regarding minimal clinical important difference
Quality of life component was also measured but followup data were not reported.

‡ However, based on figure displaying TIQ physical condition scores every 3 months, the difference between 5-ASA and placebo appears to be widest at 24 months, while it was narrowest at 21 months.

# Score developed for this study. Ten domains, each ranging from 0-6 (most severe): 1) abdominal pain, 2) abdominal tenderness, 3) bloating, 4) urgency without bowel movement, 5) diarrhea, 6) constipation. 7) painful straining with bowel movement, 8) nausea/vomiting, 9) mucus in stool, 10) dysuria. The study based its power calculation on a 30% difference in change in GSS scores between groups (or 2 points).
### Table 13. Nonsurgical treatments to prevent recurrence: Categorical outcomes not meta-analyzed*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, PMID</th>
<th>Time (mo)</th>
<th>Arm</th>
<th>n/N</th>
<th>Effect Size</th>
<th>Reported P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA vs. placebo</td>
<td><strong>Surgery for recurrent diverticulitis</strong></td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) x 12 wk</td>
<td>2/40 (5.0)</td>
<td>OR 2.11 (0.18, 24.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>1/41 (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Probiotics vs. placebo</strong></td>
<td>Diverticulitis recurrence</td>
<td>Kvasnovsky, 2017, 28528364</td>
<td>3</td>
<td>Probiotics (Symprove 1 mL/kg/d)</td>
<td>3/71 (4.2)</td>
<td>OR 0.09 (0.03, 0.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>23/72 (31.9)</td>
<td></td>
</tr>
<tr>
<td>(5-ASA + probiotics) vs. placebo</td>
<td>Diverticulitis recurrence</td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) + probiotics x 12 wk</td>
<td>10/27 (37.0)</td>
<td>OR 1.31 (0.43, 3.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>9/29 (31.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery for recurrent diverticulitis</td>
<td>Stollman, 2013 23426454</td>
<td>12</td>
<td>5-ASA (2.4 g/d) + probiotics x 12 wk</td>
<td>0/36 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>1/41 (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Rifaximin vs. placebo</strong></td>
<td>Diverticulitis recurrence</td>
<td>Lanas, 2013, 23092785</td>
<td>NR</td>
<td>Rifaximin (800 mg/d) 1 wk/mo + fiber 7 g/d</td>
<td>8/77 (10.4)</td>
<td>Adj OR 0.31 (0.11, 0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo + fiber 7 g/d</td>
<td>17/88 (19.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalization for diverticulitis</td>
<td>Lanas, 2013, 23092785</td>
<td>NR</td>
<td>Rifaximin (800 mg/d) 1 wk/mo + fiber 7 g/d</td>
<td>2/77 (2.6)</td>
<td>OR 0.36 (0.07, 1.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo + fiber 7 g/d</td>
<td>6/88 (6.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Burdock tea vs. no treatment</strong></td>
<td>Diverticulitis recurrence</td>
<td>Mizuki, 2019, 31043657</td>
<td>30</td>
<td>Burdock tea (4.5 g/d)</td>
<td>5/47 (10.6)</td>
<td>OR 0.26 (0.08, 0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No intervention</td>
<td>14/44 (31.8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 5-ASA = 5-aminosalicylic acid, Adj = adjusted, CI = confidence interval, d = days, HR = hazard ratio, mo = months, NR = not reported, OR = odds ratio, PMID = PubMed identifier, RR = risk ratio.

* For comparisons between active therapies (e.g., combination 5-ASA plus rifaximin vs. rifaximin), see Appendix Table D-4ab-1.

### Probiotics Versus Placebo

One RCT (Kvasnovsky 2017) compared the probiotic Symprove (1 mL/kg/day) with placebo in 143 participants.  

The trial reported substantially lower **diverticulitis recurrence** rates at 3 months among patients in the probiotics arm than in the placebo arm (OR 0.09, 95% CI 0.03 to 0.33) (Table 13).

### Rifaximin Versus Placebo

One RCT (Lanas 2013) compared rifaximin (800 mg/day, 1 week per month) with placebo in 165 participants. All participants also ingested daily fiber.
The trial reported substantially lower diverticulitis recurrence rates at 12 months among patients in the rifaximin arm than in the placebo arm after adjusting for age, sex, duration and localization of illness, time from last episode, and center recruitment rate (adj OR 0.31, 95% CI 0.11 to 0.86) (Table 13). The study was underpowered for hospitalization for diverticulitis, providing an imprecise comparison (OR 0.36, 95% CI 0.07 to 1.86).

5-ASA Plus Probiotics Versus Placebo

One RCT (Stollman 2013), a three-arm study, compared combination 5-ASA (2.4 g/d) plus probiotics (Bifidobacterium infantis 35624) for 12 weeks with placebo.

At 12-month followup, similar numbers of patients had episodes of diverticulitis recurrence, yielding an imprecise OR = 1.31 (95% CI 0.43 to 3.96) (Table 13). Patients on combination therapy went 181 days longer in time to diverticulitis recurrence than with placebo (Table 12), but the difference between treatments was implicitly nonsignificant, further implying a very wide confidence interval.

No patients (of 36) on combination therapy had surgery for recurrent diverticulitis, compared with 1 of 41 on placebo. Lower percentages of patients on combination therapy had GSS response or complete GSS response (see 5-ASA Versus Placebo/Symptom Scores section, above, for descriptions) than with placebo, but none of the differences was described as statistically significant (see Appendix Table D-4ab-1). The changes in GSS score were nonsignificantly different between interventions (Table 12).

Burdock Tea Versus No Treatment

One RCT (Mizuki 2019) compared the use of burdock tea (1.5 g three times a day) with no intervention in 91 patients. Burdock tea is a diuretic and antipyretic tea commonly used in Asian medicine.

The trial reported substantially lower rates of diverticulitis recurrence over a median observation period of 30 months among patients in the burdock tea arm than in the no intervention arm (OR 0.26, 95% CI 0.08 to 0.78) (Table 13). In addition, patients in the burdock tea arm were free of diverticulitis symptoms for a mean of 14.2 (95% CI 4.53 to 23.9) more months than those in the no intervention arm (Table 12).

Combination 5-ASA + Rifaximin Versus Rifaximin Alone

One RCT (Tursi 2002) compared use of a combination of balsalazide (1.6 g/day) and rifaximin (800 mg/day) with use of rifaximin alone (800 mg/day, all for 7 d/mo) in 218 participants. Balsalazide is metabolized to 5-ASA in the colon.

The comparison between intervention treatments of 12-month mortality was imprecise, with one death in each study group (Appendix Table D-4ab-1). Combination 5-ASA and rifaximin resulted in lower rates of recurrence of diverticulitis at 12 months compared with rifaximin alone (OR 0.13, 95% CI 0.04 to 0.44) (Appendix Table D-4ab-1).

About twice as many patients taking combination 5-ASA and rifaximin were symptom-free at 12 months compared with rifaximin alone (relative risk [RR] 2.02, 95% CI 1.58 to 2.58) (Appendix Table D-4ab-1), with similar findings at 3, 6, and 9 months.

Rifaximin Versus 5-ASA

One NRCS (Festa 2017) compared the use of rifaximin (800 mg/day) with use of 5-ASA (2.4 g/day), each for 10 days/month in 124 participants.
Festa 2017 reported that patients in the rifaximin arm had lower rates of recurrence of diverticulitis compared with patients in the 5-ASA arm (adjusted HR 0.27, 95% CI 0.10 to 0.72) (Table Appendix Table D-4ab-1).

5-ASA Plus Probiotics Versus 5-ASA Alone

One RCT (Stollman 2013) compared combination mesalamine (2.4 g/d) and probiotics (*Bifidobacterium infantis* 35624) with mesalamine alone, each daily for 12 weeks, with 12-month followup.125

The trial was underpowered for recurrence of diverticulitis, resulting in an imprecise comparison (OR 1.50, 95% CI 0.50 to 4.50) (Table Appendix Table D-4ab-1). Time to recurrence of diverticulitis was similar between arms (280.7 vs. 308.7 days, combination vs. 5-ASA) (Appendix Table D-4ab-2). There was no significant difference in numbers of patients who had surgery for recurrent diverticulitis (0/36 vs. 2/40).

As described under 5-ASA Versus Placebo/Symptom Scores, the study reported changes in a GSS. Data were incompletely reported but found that GSS scores were lower (better) with 5-ASA than combination 5-ASA plus probiotics at all followup timepoints, but nonsignificantly so (Appendix Table D-4ab-2). Rates of GSS response (29.2% vs. 50%) and complete GSS response (8.3% vs. 40.7%) were considerably higher with 5-ASA alone than combination therapy, but the study does not report that the difference was statistically significant (Appendix Table D-4ab-1).

5-ASA Plus Probiotics Versus Probiotics Alone

One RCT (Tursi 2007) compared combination balsalazide (2.25 g/d) and probiotics (VSL #3) with use of probiotics alone, each for 15 days/month.131

The trial was underpowered for recurrence of diverticulitis, resulting in an imprecise comparison (OR 0.38, 95% CI 0.07 to 1.92) (Appendix Table D-4ab-1).

Adverse Events

Serious Adverse Events

Five RCTs (the PREVENT-1, PREVENT-2, SAG-37, Parente 2013, Stollman 2013) evaluating a variety of doses of 5-ASA (ranging from 0.8 to 4.8 g/day) reported adverse events that the authors named as serious. However, they did not define the outcome (Table 14). Serious adverse event rates ranged between 8 and 14 percent across 5-ASA arms. But in all trials, similar serious adverse event rates were seen in the placebo groups.

Other Adverse Events

Three RCTs (PREVENT-1, PREVENT-2, Stollman 2013), which compared 1.2 to 4.8 g/day doses of 5-ASA with placebo, reported on specific adverse events, namely sepsis, acute myocardial infarction, and urinary tract infections. Sepsis and acute myocardial infarction were rare (Table 14). No differences were found in rates of urinary tract infections between each of the 5-ASA groups and placebo. The single group study (Silva Sanchez 2014) also found a similar rate of urinary tract infections as in the two trials. Stollman 2013 reported no headaches in either the 5-ASA or placebo arm; Silva Sanchez 2014 reported that 9.0 percent of patients taking 5-ASA complained of headache (without a comparator group).
Adverse Events Leading to Discontinuation

Three RCTs (SAG-37, Parente 2013, Stollman 2013) reported on adverse events that led to discontinuation (Table 14). All RCTs reported that, compared with placebo, 5-ASA use was associated with a higher likelihood of discontinuation due to adverse events, but while the SAG-37 trial found a statistically significant difference, the other two trials were (near) imprecise.

Table 14. Adverse events of 5-ASA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, PMID</th>
<th>Arm</th>
<th>n/N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious AEs</strong></td>
<td>PREVENT-1 2014</td>
<td>5-ASA (4.8 g/d)</td>
<td>18/150  (12.0)</td>
<td>1.12 (0.55, 2.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (2.4 g/d)</td>
<td>15/143  (10.5)</td>
<td>0.96 (0.46, 2.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (1.2 g/d)</td>
<td>16/143  (11.2)</td>
<td>1.03 (0.49, 2.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>16/147  (10.9)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>PREVENT-2 2014</td>
<td>5-ASA (All doses)</td>
<td>36/444  (8.1)</td>
<td>0.75 (0.40, 1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>15/142  (10.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAG-37 2017</td>
<td>5-ASA (3.0 g/d)</td>
<td>55/387  (14.2)</td>
<td>1.46 (0.91, 2.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>29/285  (10.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parente, 2013, 23754545</td>
<td>5-ASA (800 mg/d)</td>
<td>4/45    (8.9)</td>
<td>2.20 (0.38, 12.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>2/47    (4.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stollman, 2013 23426454</td>
<td>5-ASA (2.4 g/d)</td>
<td>5/40    (12.5)</td>
<td>1.81 (0.40, 8.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>3/41    (7.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>PREVENT-1 2014</td>
<td>5-ASA (4.8 g/d)</td>
<td>1/150   (0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (2.4 g/d)</td>
<td>0/143   (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (1.2 g/d)</td>
<td>1/143   (0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>0/147   (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Acute myocardial infarction</strong></td>
<td>PREVENT-1 2014</td>
<td>5-ASA (4.8 g/d)</td>
<td>0/150   (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (2.4 g/d)</td>
<td>0/143   (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (1.2 g/d)</td>
<td>1/143   (0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>2/147   (1.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary tract infection requiring antibiotics</strong></td>
<td>PREVENT-1 2014</td>
<td>5-ASA (4.8 g/d)</td>
<td>8/150   (5.3)</td>
<td>0.43 (0.18, 1.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (2.4 g/d)</td>
<td>12/143  (8.4)</td>
<td>0.70 (0.32, 1.52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (1.2 g/d)</td>
<td>14/143  (9.8)</td>
<td>0.83 (0.39, 1.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>17/147  (11.6)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>PREVENT-2 2014</td>
<td>5-ASA (4.8 g/d)</td>
<td>10/149  (6.7)</td>
<td>1.39 (0.51, 3.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (2.4 g/d)</td>
<td>14/147  (9.5)</td>
<td>2.03 (0.79, 5.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-ASA (1.2 g/d)</td>
<td>11/148  (7.4)</td>
<td>1.55 (0.58, 4.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>7/142   (4.9)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Stollman, 2013 23426454</td>
<td>5-ASA (2.4 g/d)</td>
<td>1/40    (2.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>0/41    (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silva Sanchez, 2014, No PMID</td>
<td>5-ASA (4.8 g/d)</td>
<td>18/299  (6.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>Stollman, 2013 23426454</td>
<td>5-ASA (2.4 g/d)</td>
<td>0/40    (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>0/41    (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silva Sanchez, 2014, No PMID</td>
<td>5-ASA (4.8 g/d)</td>
<td>27/299  (9.0)</td>
<td></td>
</tr>
<tr>
<td><strong>AEs leading to discontinuation</strong></td>
<td>SAG-37 2017</td>
<td>5-ASA (3.0 g/d)</td>
<td>97/387  (25.1)</td>
<td>OR 1.53 (1.05, 2.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>51/285  (17.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parente, 2013, 23754545</td>
<td>5-ASA (800 mg/d)</td>
<td>8/45    (17.8)</td>
<td>OR 2.32 (0.65, 8.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>4/47    (8.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stollman, 2013 23426454</td>
<td>5-ASA (2.4 g/d)</td>
<td>5/40    (12.5)</td>
<td>OR 1.81 (0.40, 8.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>3/41    (7.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 5-ASA = 5-aminosalicylic acid, AE = adverse event, CI = confidence interval, OR = odds ratio, PMID = PubMed identifier.

Summary of Evidence Pertaining to Nonsurgical Interventions

The evidence profile (Table 15) summarizes the findings for which there is sufficient evidence, which were only risk of diverticulitis recurrence and adverse events from 5-ASA treatment.

Eleven studies evaluated various nonsurgical interventions to prevent recurrent diverticulitis. However, except for the comparison between 5-ASA and placebo, only a single study evaluated
each intervention or comparison. Notably, no comparative study evaluated medical nutrition therapy.

The most extensively evaluated treatment is 5-ASA. All six RCTs that compared 5-ASA to placebo found no statistically significant difference in diverticulitis recurrence between groups. Across studies, there is high SoE that 5-ASA does not reduce risk of recurrence. The summary OR actually nominally favored placebo with an OR of 1.15 (95% CI 0.92 to 1.44) suggesting a higher risk of recurrence with 5-ASA treatment. No differences in effect were seen based on the different doses of 5-ASA tested (ranging from 1.2 to 4.8 g/day). Evidence about time to recurrence was conflicting among three studies (insufficient evidence). Evidence about undergoing surgery for recurrent diverticulitis, and symptoms scores are sparse (insufficient evidence). There is high SoE (6 studies) that reports of adverse events are similar among patients taking 5-ASA or placebo.

Other interventions were evaluated by only a single study each; thus, all with insufficient evidence.
Table 15. Evidence profile for nonsurgical interventions to prevent recurrence

<table>
<thead>
<tr>
<th>Topic</th>
<th>No. Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Conclusion statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA to prevent recurrence (vs. placebo)</td>
<td>6 (1898)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>5-ASA does not reduce the risk of recurrence OR 1.15 (0.92, 1.44), nominally favoring placebo</td>
</tr>
<tr>
<td>5-ASA adverse events</td>
<td>6 (1898)</td>
<td>Low</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High</td>
<td>Adverse events are no more common with 5-ASA than placebo</td>
</tr>
<tr>
<td>Other treatments to prevent recurrence*</td>
<td>7 (30-218)</td>
<td>Moderate</td>
<td>N/A</td>
<td>Mixed</td>
<td>Direct</td>
<td>Sparse†</td>
<td>Insufficient</td>
<td>No conclusions</td>
</tr>
</tbody>
</table>

Abbreviations: N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

* Rifaximin, probiotics, combination 5-ASA and rifaximin, combination 5-ASA and probiotics, and burdock tea

† Each study made a unique comparison.
Key Question 4c. Elective Surgery

Key Points

- Recurrence of diverticulitis in patients with either recurrent or complicated diverticulitis was about 5- to 7-times lower among those who underwent elective surgery than those treated medically (high SoE).
- The 30-day mortality rate was 0.7% across studies (moderate SoE). Specific serious adverse events were uncommon with elective surgery (low to moderate SoE). The most common adverse events were reoperation (5.5%) and anastomotic leakage (4.3%) (both low SoE). Other adverse events occurred in less than 2% of patients (low to moderate SoE).
- There was insufficient evidence to allow conclusions for other outcomes.

Findings Pertaining to Elective Surgery

Elective Surgery Compared to Nonoperative Management

Two small RCTs in four reports and one large NRCS with adjusted analyses evaluated elective surgery (laparoscopic sigmoid colectomy, laparoscopic sigmoidectomy, and colectomy) compared to nonoperative management. Nonoperative management was described as conservative management, observation, or simply nonoperative management. The NRCS conducted propensity score adjusted analyses on some of their reported outcomes.

Full baseline data is in Appendix C Tables C-4c-1 to C-4c-5; Appendix D, Tables D-4c-1 to D-4c-3 provide study-level results. The RCTs each enrolled just over 100 participants with a previous episode of acute diverticulitis. However, the two RCTs included different patients. The DIRECT trial (van de Wall 2017) included patients with uncomplicated disease who had either smoldering symptoms (persisting >3 months) or frequent recurring symptoms (≥3 within 2 years) while You 2018 evaluated patients with a history of complicated diverticulitis manifested as extraluminal air with or without abscess (although not statistically different, 58% of patients in the surgery arm had a history of an abscess while only 42% did in the observation group). The NRCS (Aquila 2019) included 7072 patients with a history of an acute diverticular abscess (complicated diverticulitis).

Participant ages were similar across studies, with participants in their mid 50s, and between 28 and 54 percent were male across studies. One RCT was industry funded (You 2018), the other was non-industry funded; the NRCS did not report funding source. Both RCTs were of low risk of bias for randomization, incomplete outcome data, and selective reporting, but high risk of bias for blinding. The NRCS had a low risk of bias for confounding and selection bias. Full risk of bias in Appendix C; full results are in Appendix D.

Mortality

The You 2018 and DIRECT RCTs reported mortality at 3 and 5 years, respectively (Table 16). In both studies, there were no deaths in the elective surgery arms and one death (total) in the nonoperative treatment arm. The studies were underpowered to evaluate mortality within 3 to 5 years.
The NRCS (Aquina 2019) reported an unadjusted analysis of diverticulitis-related death, but found a large difference. The death rate was substantially lower in the elective surgery group (0.2%) at 5 years than the nonsurgical treatment group (1.9%), implying an unadjusted OR of 0.13 (95% CI 0.03 to 0.29), suggesting the number needed to treat (NNT) to prevent one death was 57 (95% CI 46 to 76). Note that strictly speaking, this analysis does not meet criteria for being included in the review because the analysis was unadjusted for underlying differences between people who do and do not undergo elective surgery. However, we include it because it is the largest study, by far, that directly compares elective surgery to no surgery.

Table 16. Elective surgery versus no surgery: Categorical outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>PMID</th>
<th>Followup Time</th>
<th>Arm</th>
<th>n/N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>You 2018</td>
<td>29683483</td>
<td>3 y</td>
<td>Elective surgery</td>
<td>0/26 (0)</td>
<td>0 events</td>
</tr>
<tr>
<td></td>
<td>DIRECT 2017</td>
<td>28404008</td>
<td>5 y</td>
<td>Elective surgery</td>
<td>0/53 (0)</td>
<td>0.51 (0.02, 15.6)</td>
</tr>
<tr>
<td></td>
<td>Aquina 2019</td>
<td>30335195</td>
<td>5 y</td>
<td>Elective surgery</td>
<td>3/1660 (0.2)</td>
<td>0.09 (0.03, 0.29)</td>
</tr>
<tr>
<td></td>
<td>DIRECT 2017</td>
<td>28404008</td>
<td>5 y</td>
<td>No surgery</td>
<td>1/56 (1.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aquina 2019</td>
<td>30335195</td>
<td>5 y</td>
<td>No intervention</td>
<td>104/5412 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Diverticulitis recurrence</td>
<td>You 2018</td>
<td>29683483</td>
<td>3 y</td>
<td>Elective surgery</td>
<td>2/26 (7.7)</td>
<td>0.18 (0.04, 0.80)</td>
</tr>
<tr>
<td></td>
<td>DIRECT 2017</td>
<td>28404008</td>
<td>5 y</td>
<td>Elective surgery</td>
<td>6/53 (11.3)</td>
<td>0.29 (0.11, 0.81)</td>
</tr>
<tr>
<td></td>
<td>Aquina 2019</td>
<td>30335195</td>
<td>5 y</td>
<td>Elective surgery</td>
<td>70/1660 (4.2)</td>
<td>0.13 (0.10, 0.17)</td>
</tr>
<tr>
<td></td>
<td>DIRECT 2017</td>
<td>28404008</td>
<td>5 y</td>
<td>No surgery</td>
<td>17/56 (30.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aquina 2019</td>
<td>30335195</td>
<td>5 y</td>
<td>No surgery</td>
<td>1340/5412 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Stoma</td>
<td>Aquina 2019</td>
<td>30335195</td>
<td>5 y</td>
<td>Elective surgery</td>
<td>166/1660 (10.0)</td>
<td>1.88 (1.50, 2.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No surgery</td>
<td>309/5412 (5.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, PMID = PubMed identifier, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, y = year.

Recurrence

The two RCTs found that at 3 and 5 years, elective surgery had substantially lower rates of recurrence than nonoperative treatment (Table 16) One RCT (You 2018) of 107 people with a first episode of acute diverticulitis complicated by extraluminal air and with or without abscess, which had initially been treated with successful nonoperative management, reported an OR of 0.18 (95% CI 0.04 to 0.80) favoring surgery. The second RCT (DIRECT 2017) of 109 people with either ongoing abdominal complaints or frequently recurring left-sided diverticulitis (mean number of recurrences 3.61 [SD 1.67]) reported an OR of 0.29 (95% CI 0.11 to 0.81) favoring surgery. The You 2018 RCT also reported that time to recurrence (Table 17) was significantly longer in the elective surgery arm (median 11 months) than the nonoperative treatment arm (median 7 months; P=0.015).

The NRCS (Aquina 2019) reported an unadjusted analysis of recurrence rates (Table 16), but found a large difference. The recurrence rate was substantially lower in the elective surgery group (4.2%) than the nonsurgical treatment group (24.8%), implying an unadjusted OR of 0.13 (95% CI 0.10 to 0.17), suggesting the number needed to treat (NNT) to prevent one recurrence was 4.9 (95% CI 4.5 to 5.3). Similar to the mortality analysis, this analysis does not meet criteria for being included in the review (since it was unadjusted), but, we include it because it is the largest study, by far, that directly compares elective surgery to no surgery..

---

III Unadjusted odds ratio from a nonrandomized comparative study.
II Unadjusted odds ratio from a nonrandomized comparative study.
II Unadjusted odds ratio from a nonrandomized comparative study.
Although the NRCS did not report an adjusted analysis, *post hoc*, we decided to meta-analyzed the three studies based on their similar results. As shown in Figure 11, the summary OR was 0.16 (95% CI 0.09 to 0.27).

**Table 17. Elective surgery versus no surgery: Continuous outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Arm</th>
<th>N</th>
<th>Results</th>
<th>Difference (95% CI)</th>
<th>Reported P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recurrence</td>
<td>You 2018</td>
<td>Elective surgery</td>
<td>26</td>
<td>Median 11 mo (IQR 8, 14)</td>
<td>4 mo&lt;sup&gt;LL&lt;/sup&gt;</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No surgery</td>
<td>81</td>
<td>Median 7 mo (IQR 3.25, 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>You 2018</td>
<td>Elective surgery</td>
<td>26</td>
<td>Median 5.5 d (IQR 4, 8.5)</td>
<td>0.5 d&lt;sup&gt;MM&lt;/sup&gt;</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No surgery</td>
<td>81</td>
<td>Median 5 d (IQR 4, 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aquina 2019</td>
<td>Elective surgery</td>
<td>1660</td>
<td>Mean 8.0 d (SD 7.8)</td>
<td>Adj IRR = 2.16 (1.89, 2.47)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No surgery</td>
<td>5412</td>
<td>Mean 4.6 d (SD 18.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Adj = adjusted, IRR = “incidence rate ratio” (ratio of means), CI = confidence interval, d = days, IQR= interquartile range, mo = months, PMID = PubMed identifier, SD = standard deviation.

**Figure 11. Meta-analysis of elective surgery for diverticulitis versus no surgery: Recurrence of diverticulitis**

![Figure 11. Meta-analysis of elective surgery for diverticulitis versus no surgery: Recurrence of diverticulitis](image)

Abbreviations: CI = confidence interval, F/up = followup, I² = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NRCS, unadj = unadjusted nonrandomized comparative study, OR = odds ratio, P<sub>het</sub> = statistical heterogeneity P value.

**Stoma**

The NRCS (Aquina 2019) reported a propensity score-adjusted comparison of stoma rates among patients who underwent elective surgery versus those who received nonoperative management. In the operative group, stomas were created during their elective surgery. In the nonoperative group, stomas were created during diverticulitis-related admissions during the 5 year followup period. As predicted by the researchers, those receiving elective surgery were more likely to have a stoma created, with an adjusted OR of 1.88 (95% CI 1.50 to 2.36).

**Length of Hospital Stay**

Two studies reported on length of hospital stay (Table 17). In the You 2018 RCT there was no difference in length of stay between elective surgery (median 5.5 days) and nonoperative management (median 5 days). In the Aquina 2019 NRCS, the elective surgery arm had a longer mean length of stay at 8 days compared to the nonoperative treatment arm (4.6 days). The propensity-score adjusted ratio of the length of stay (operative/nonoperative) was 2.16 (95% CI

<sup>KK</sup> Quality of life and pain (visual analog scale) results are reported in Appendix D Table D-4c-2.

<sup>LL</sup> Difference of median values. Confidence interval not estimated.

<sup>MM</sup> Difference of median values. Confidence interval not estimated.
Quality of Life and Pain

The DIRECT 2017 RCT reported on quality of life and pain in 109 participants (Appendix D Table D-4c-2). Across four scales (GIQLI, SF-36 mental and physical, and EQ-5DNN), people in the elective surgery group had greater improvements in quality of life and pain measures at both 6 months and 5 years, compared with baseline.

On the GIQLI scale at 6 months, the net difference (difference-in-difference) between arms from baseline was 13.6 units (95% CI 5.2 to 22.0; P=0.0001) on a scale from 0 to 144 where higher scores are desirable. At 5 years, the net difference between arms from baseline was 9.3 (95% CI 1.3, to 17.3; P=0.018).

On the SF-36 mental health scale at 6 months, the net difference between arms from baseline was 4.1 units (95% CI −0.4 to 8.6; P=0.26) on a scale of 0 to 100, with higher scores indicating better quality of life. At 5 years, there was a statistically significant net difference between arms from baseline of 6.4 (95% CI 2.2, to 10.6; P=0.010). On the SF-36 physical health scale at 6 months, the net difference between arms from baseline was 3.9 units (95% CI 1.1 to 6.7; P=0.016) and at 5 years 4.9 units (95% CI 1.5, to 8.3; P=0.030).

On the EQ-5D scale (0 to 1, with 1 reflecting best possible health) at both 6 months and 5 years, the net differences between arms from baseline were 0.16 units (95% CI 0.08 to 0.24; P=0.001).

On the VAS scale for pain (0-100, with 0 = no pain), the net difference at 6 months was −18.4 units (95% CI −26.4 to −10.4; P<0.0001) and at 5 years −11.0 (95% CI −20.1 to −1.9; P=0.011) favoring elective surgery.

The authors report these differences to be “clinically measurable,” and the GIQLI differences are above the published minimal clinically important differences (MCID) in a GIQLI validation study in cholecystectomy patients. A systematic review suggests that for a category that includes gastroenterology, the differences reported in this paper are above the high range of the MCID for the GIQLI, SF-36, and EQ-5D. Finally, the net difference on the VAS scale was above that determined to indicate a clinically important difference in patients recovering from surgery.

Notably, none of the studies evaluated psychosocial outcomes such as anxiety, stress, or fear related to the risk of recurrent episodes of acute diverticulitis.

Adverse Events Associated with Elective Surgery

Serious adverse events associated with elective surgery were reported in 17 studies (2 RCTs, 1 NRCS, and 14 eligible single-group studies in 15 reports). We did not review nonserious adverse events. Of note, for the purpose of this review, single group studies are studies of elective surgery without a comparison to nonsurgical management. Thus, studies that compared two or more specific surgeries, but no nonsurgical group, were considered to be single group studies of surgery. As relevant, we note differences between surgeries, but this was not a question of interest, per se.

The characteristics of the comparative studies are described above. The single-group studies were all either non-industry funded or did not report funding source. The inclusion criteria were either having undergone elective surgery for diverticulitis (15 studies) or having a diagnosis of
diverticulitis (2 studies). Very few studies reported on time between acute diverticulitis incident and surgery or number of prior episodes of diverticulitis. The median percentage of men across studies was 47 percent (range 29 to 52, and the mean age ranged from 55 to over 76. Surgeries included sigmoidectomy or left colectomy (with or without stoma). Most surgeries were reported to be laparoscopic or not reported, but in one study all surgeries were open\textsuperscript{143, 154} and in another study 28 percent were open.\textsuperscript{145} Full baseline data are in Appendix C Tables C-4c-1 to C-4c-5.

Risk of bias was low in all studies for incomplete outcome data, prespecification of eligibility criteria, and prespecification and clear measurement of outcomes. One study had a high risk of bias for selective outcome reporting,\textsuperscript{143, 154} and in another it was unclear.\textsuperscript{149} Two studies had a high risk of bias unclear reporting of the intervention.\textsuperscript{141, 142}

**Overall Adverse Event Rates**

In general, composite adverse events (of multiple events) were common, but individual adverse event rates were low. Each specific adverse event was reported by only a small subset of the 18 included studies. The most commonly reported adverse event was 30-day mortality, which was reported by nine studies. Five adverse events were reported by five to seven studies (sepsis, unplanned reoperation, anastomotic leakage, myocardial infarction, and pulmonary embolism). Ten listed adverse events were reported by only one or two studies. Given the frequently large range of adverse event rates across studies, it is likely that the estimates derived from small numbers of studies are likely to change with future evidence.

We summarize the adverse events in Table 18, where adverse events are sorted by their frequency (full results are in Appendix D Table D-4c-3). For the purpose of providing a single, if rough, estimate of specific adverse event rates, we meta-analyzed outcomes when at least two studies (or cohorts) reported the same adverse event, regardless of the possible lack of commonality of populations, surgeries, or specific adverse event definitions. To demonstrate heterogeneity (differences across studies), we also provide the range of specific adverse event rates reported across studies. When articles reported adverse event rates for different cohorts (e.g., different specific surgeries) separately, we treated each cohort as a separate study for the purpose of meta-analysis.

Across a subset of four of the 18 studies, 25 percent of patients undergoing elective surgery had some serious adverse event; although, the definitions of serious adverse events were generally unclear and likely varied widely (and likely included nonserious adverse events) as the range of event rates was 4 to 70 percent.

Of the individual adverse events, 30-day mortality was 0.7 percent across nine studies; 30-day readmission was 7.3 percent across three studies. Other common adverse events included major pulmonary events (7.8% in one study) and reoperation (5.5% across 6 studies). All outcomes are listed in Table 18.

Although, likely not strictly an adverse event, we note that in one study, 12.6 percent of patients had unplanned or planned ostomies.
Table 18. Adverse events of elective surgery

<table>
<thead>
<tr>
<th>Adverse Event (Clavien-Dindo Classification, As Applicable)</th>
<th>n/N (Total)</th>
<th>Summary Percentage (95% CI)</th>
<th>Range Across Studies</th>
<th>Evidence base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE (composite or not otherwise specified)</td>
<td>544/2928</td>
<td><strong>25.1 (3.7, 57.0)</strong></td>
<td>4.0 – 69.8</td>
<td>4 studies&lt;sup&gt;132-135, 149, 150&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ostomy (either planned or unplanned, implied)</td>
<td>3006/23,752</td>
<td>12.6 (12.2, 13.1)</td>
<td>12.6</td>
<td>1 study&lt;sup&gt;143, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Major pulmonary event, composite (CD IV) (Respiratory tract complications, acute bacterial pneumonia, acute respiratory failure)</td>
<td>1782/22,752</td>
<td>7.8 (7.5, 8.2)</td>
<td>7.8</td>
<td>1 study&lt;sup&gt;143, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>30-day readmission (CD IV)</td>
<td>983/14,380</td>
<td>7.3 (3.8, 11.8)</td>
<td>4.2 – 11.0</td>
<td>3 studies&lt;sup&gt;145, 149, 153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reoperation, unplanned (CD III)</td>
<td>4256/49,004</td>
<td><strong>5.5 (3.1, 8.5)</strong></td>
<td>0 – 12.7</td>
<td>6 studies&lt;sup&gt;132, 142, 143, 145, 150, 152, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anastomotic leakage requiring procedure (CD III)</td>
<td>1077/15,367</td>
<td><strong>4.3 (2.2, 6.9)</strong></td>
<td>1.5 – 13.2</td>
<td>6 studies&lt;sup&gt;133-135, 147, 151&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urinary tract infections requiring antibiotics (CD II)</td>
<td>84/3079</td>
<td>3.9 (1.6, 7.2)</td>
<td>2.1 – 7.5</td>
<td>3 studies&lt;sup&gt;133-135, 147, 152&lt;/sup&gt;</td>
</tr>
<tr>
<td>Small bowel obstruction requiring procedure (CD III)</td>
<td>1/26</td>
<td>3.8 (0.5, 22.8)</td>
<td>3.8</td>
<td>1 study&lt;sup&gt;132&lt;/sup&gt;</td>
</tr>
<tr>
<td>C diff infection</td>
<td>17/576</td>
<td>3.0 (1.8, 4.7)</td>
<td>3.0</td>
<td>1 study&lt;sup&gt;140&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>879/34,526</td>
<td>2.0 (0.7, 3.9)</td>
<td>0.7 – 3.4</td>
<td>3 studies&lt;sup&gt;142, 143, 147, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary edema (CD IV)</td>
<td>10/582</td>
<td>1.7 (0.9, 3.2)</td>
<td>1.7</td>
<td>1 study&lt;sup&gt;147&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incisional hernia requiring procedure (CD III)</td>
<td>10/576</td>
<td>1.7 (0.9, 3.2)</td>
<td>1.7</td>
<td>1 study&lt;sup&gt;140&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sepsis (CD IV)</td>
<td>1719/82,597</td>
<td><strong>1.6 (1.0, 2.3)</strong></td>
<td>0.6 – 2.9</td>
<td>7 studies&lt;sup&gt;142, 143, 145-148, 152, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surgical site infections requiring antibiotics (CD II)</td>
<td>40/3272</td>
<td><strong>1.4 (0.8, 1.9)</strong></td>
<td>0.9 – 4.0</td>
<td>4 studies&lt;sup&gt;132, 140, 144, 147&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia (CD IV)</td>
<td>48/14,218</td>
<td>1.3 (0.4, 4.4)</td>
<td>0.8 – 4.5</td>
<td>3 studies&lt;sup&gt;142, 147, 152&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ileus</td>
<td>30/2294</td>
<td>1.3 (0.1, 3.8)</td>
<td>0.2 – 4.0</td>
<td>3 studies&lt;sup&gt;132, 140, 151&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intra-abdominal abscess (CD IV)</td>
<td>138/11,192</td>
<td>1.2 (1.0, 1.5)</td>
<td>1.2</td>
<td>1 study&lt;sup&gt;142&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bleed requiring transfusion (CD II)</td>
<td>515/27,946</td>
<td>1.1 (0.6, 1.8)</td>
<td>0.7 – 2.0</td>
<td>3 studies&lt;sup&gt;143, 148, 151, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (CD IV)</td>
<td>114/11,192</td>
<td>1.0 (0.8, 1.2)</td>
<td>1.0</td>
<td>1 study&lt;sup&gt;142&lt;/sup&gt;</td>
</tr>
<tr>
<td>30-day mortality (CD V)</td>
<td>4957/199,915</td>
<td><strong>0.7 (0.3, 1.4)</strong></td>
<td>0.18 – 3.5</td>
<td>9 studies&lt;sup&gt;136, 142, 143, 145-149, 151, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial infarction (CD IV)</td>
<td>702/65,459</td>
<td><strong>0.7 (0.1, 1.6)</strong></td>
<td>0.2 – 2.5</td>
<td>5 studies&lt;sup&gt;143, 145-148, 152, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac arrest (CD IV)</td>
<td>160/25,205</td>
<td>0.6 (0.1, 1.7)</td>
<td>0.1 – 1.9</td>
<td>3 studies&lt;sup&gt;133-135, 144, 146&lt;/sup&gt;</td>
</tr>
<tr>
<td>DVT</td>
<td>293/36,970</td>
<td><strong>0.6 (0.2, 1.1)</strong></td>
<td>0.2 – 1.1</td>
<td>4 studies&lt;sup&gt;142, 143, 147, 152, 154&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reintubation (CD IV)</td>
<td>282/39,681</td>
<td>0.6 (0.4, 0.9)</td>
<td>0.5 – 0.8</td>
<td>2 studies&lt;sup&gt;143, 146&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke (CD IV)</td>
<td>3/582</td>
<td>0.5 (0.2, 1.6)</td>
<td>0.5</td>
<td>1 study&lt;sup&gt;147&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary embolism (CD IV)</td>
<td>167/43,818</td>
<td><strong>0.3 (0.1, 0.6)</strong></td>
<td>0.2 – 3.8</td>
<td>5 studies&lt;sup&gt;133-135, 145-148&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Adverse events reported by at least four studies are noted in bold font.

Abbreviations: AE=adverse event; C diff = Clostridioides difficile; CD=Clavien-Dindo Classification; CPR = cardiopulmonary resuscitation; DVT=deep vein thrombosis; OR=operating room; SAE= serious adverse event.
Predictors of Adverse Events

Four of the single-arm studies reported on adverse events in various subgroups, including age, simple/complicated diverticulitis, body mass index (BMI), and comorbidities (Appendix D Table D-4c-3). 140, 149, 151, 154

Age as a Predictor

Two studies evaluated age as a predictor of various adverse events (Sheer 2011 154 and Tsilimparis 2010 151).

Risk of 30-Day Mortality

Both studies evaluated age as a predictor of 30-day mortality after elective surgery. Sheer 2011, in a study of Medicare beneficiary with an overall death rate of 1.22 percent, found that the OR for the oldest (85 and older) compared to the youngest age group (65 to 69) was 10.2 (95% CI 6.49, 16.0), and the odds increased with every age in between. Tsilimparis 2010 was underpowered for death, with only a single death, which occurred in the 70 and older subgroup. 151

Risk of Bleed

Both studies also reported on risk of bleed requiring transfusion. Sheer 2011, found inconsistent results across age groups. The overall hemorrhage rate was 2.0 percent. Compared with the youngest age group (65-69), only the 75 to 79 year subgroup had a statistically significant adjusted OR of hemorrhage (OR 1.4, 95% CI 1.09 to 1.80). The other age subgroups had adjusted ORs of 1 or 1.1 (nonsignificant). Tsilimparis 2010 reported that the event rate was 0.6 percent in the youngest age group (<60), 0 in the middle age group (60-69), and 1.9 percent in the oldest age group (>69) (P value across age groups 0.06). However, they also reported that hemorrhage requiring surgery was most common in the youngest age group (1.7%) compared with the middle group (0.4%) and no one in the oldest group.

Risk of Other Adverse Events

Other adverse events were reported by only one study each. Among evaluated adverse events, From a multivariable analysis, Sheer 2011 found evidence supportive of older age increasing risks for shock or sepsis (OR 3.5, 95% CI 2.47 to 4.98; 1.9% overall), pulmonary complications (OR 2.8, 95% CI 2.26 to 3.40; 7.2% overall), acute kidney insufficiency (OR 2.4, 95% CI 1.72 to 3.41; 2.4% overall), colostomy (OR 2.2, 95% CI 1.92 to 2.58; 9.1%), and cardiac complications (OR 2.2, 95% CI 1.59 to 3.09; 2.4% overall). Mixed findings (variable association and significance across age groups) for wound complications (4.4% overall) and ileostomy (2.2% overall). No associations were found for thromboembolic events (1.0% overall).

Tsilimparis 2010 also reported that age was not associated with risk of ileus (which occurred among 0.8% overall) or 30-day hospital readmission (3.9% overall).

Simple Versus Complicated Diverticulitis as Predictors of Adverse Events

Two studies (Bhakta 2016 and Silva-Velazco 2016) reported information on type of diverticulitis as a predictor of adverse events with elective laparoscopic surgery, but each adverse event was reported only in a single study (Appendix D Table D-4c-3). 140, 149

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Bhakta 2016 found that a history of complicated diverticulitis increased the risks of ileus (8.6% vs. 3.2%; unadjusted OR 2.85, 95% CI 1.29, 6.33). No associations were found for surgical site infection, anastomotic leak, incisional hernia, or C. diff infection.

In a multivariable analysis, Silva-Velazco, 2016 found that a history of complicated diverticulitis increased the risk of anastomotic leak and/or pelvic abscess (10.7% vs. 4.3%; OR 2.37, 95% CI 1.36 to 4.11) and may have somewhat increased the risk for overall postoperative morbidity (36% vs. 25%; OR 1.32, 95% CI 0.96 to 1.82). Postoperative morbidity included clinical anastomotic leak, abdominal and/or pelvic abscess, postoperative bleeding, deep vein thrombosis, dehydration, ileus, mechanical small bowel obstruction, small bowel leak, stoma complications, C. diff infection, sepsis, wound infection, wound dehiscence, urinary, renal, cardiovascular and other respiratory morbidities.

Other Predictors of Adverse Events

One study (Silva-Velazco 2016) reported information on body weight as a predictor of adverse events of laparoscopic surgery (Appendix D Table D-4c-3). In multivariable analyses, morbid obesity (BMI ≥35 kg/m²), but not obesity (BMI 30-35 kg/m²), was associated with a higher rate of postoperative anastomotic leak and/or abdominopelvic abscess (OR 2.30, 95% CI 1.16 to 4.55). BMI was not associated with risk of any postoperative morbidity.

One study (Sheer 2011) reported on the comorbidities chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) as predictors of a range of adverse events in multivariable analyses of patients undergoing elective laparoscopic surgery (Appendix D Table D-4c-3). COPD was associated with increased risks of pulmonary complications (OR 2.2, 95% CI 1.94 to 2.50) and wound complications (OR 1.4, 95% CI 1.19 to 1.67), but not other complications (in-hospital death, colostomy, ileostomy, hemorrhage, acute kidney insufficiency, cardiac complications, shock/sepsis, or thromboembolic events). CHF, on the other hand, was statistically significantly and strongly associated with in-hospital death (OR 3.5, 95% CI 2.59 to 4.63), cardiac complications (OR 4.6), pulmonary complications (OR 4.2), acute kidney injury (OR 4.1), shock or sepsis (OR 3.2); weakly but significantly, associated with colostomy (OR 1.9), wound infection (OR 1.9), thromboembolic event (OR 1.6), and hemorrhage (OR 1.5); but not ileostomy.

Summary of Evidence Pertaining to Elective Surgery

The evidence profile (Table 19) summarizes the findings for which there is sufficient evidence (and selected outcomes with insufficient evidence).

Two relatively small RCTs and one large NRCS (with propensity score adjustment) compared people with a history of acute diverticulitis who underwent elective surgery versus those who continued medical management. The two RCTs were in different populations (prior uncomplicated or complicated diverticulitis [extraluminal air, half with an abscess]); the NRCS was also conducted in patients with a history of complicated diverticulitis (all with an abscess). The NRCS reported some propensity-score adjusted analyses. The RCTs were too small to evaluate death, but the NRCS found a large (unadjusted) difference favoring surgery (0.2% vs. 1.9% at 5 years). With high SoE, all three studies found that about six times as many recurrences of diverticulitis occurred among those who were treated nonsurgically. However, from the NRCS, almost twice as many people who underwent elective surgery ended up with a stoma after about 5 years of followup. The one RCT and the NRCS that evaluated (total) length of hospital stay (regardless of reason for hospitalization) found conflicting results either of no
difference (in the RCT) or favoring nonoperative management (in the adjusted NRCS). One RCT found that people in the elective surgery group had better quality of life and less pain at 6 months and 5 years. No studies evaluated psychosocial outcomes.

Elective surgery for diverticulitis may be associated with frequent total serious adverse events, but the frequency across studies was highly variable (4% to 70%) and likely related to definitions of adverse events (thus, there was insufficient evidence to estimate the frequency of total serious adverse events). The most commonly reported adverse event, which was reported by 9 of 17 studies, was 30-day mortality which occurred, on average, in 0.7% of patients undergoing elective surgery (moderate SoE). The more common adverse events (that were reported by at least 4 studies) were unplanned reoperations (5.5%; low SoE) and anastomotic leakage requiring a procedure (4.3%; low SoE). Less common adverse events (reported by at least 4 studies) included sepsis (1.6%; moderate SoE), surgical site infection requiring antibiotics (1.4%; moderate SoE), myocardial infarction (0.7%; moderate SoE), deep vein thrombosis (0.6%; Moderate SoE), and pulmonary embolism (0.3%; moderate SoE).

Four studies evaluated subgroups of patients as predictors of various adverse events related to elective surgery for diverticulitis. However, each finding was based on only a single study. Strong associations (OR >2) were found for older patients and increased likelihood of death and risk for shock or sepsis, pulmonary complications, acute kidney insufficiency, colostomy, and cardiac complications. A history of complicated diverticulitis was strongly associated with ileus and, separately, anastomotic leak and/or pelvic abscess. Other strong predictors of adverse events (based on one study each) were morbid obesity and anastomotic leak and/or pelvic abscess, COPD and pulmonary complications, and CHF and in-hospital death, cardiac complications, pulmonary complications, acute kidney injury, and shock or sepsis.
### Table 19. Evidence profile for elective surgery

<table>
<thead>
<tr>
<th>Topic</th>
<th>Outcome</th>
<th>No. Studies (Subjects)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Precision</th>
<th>Directness</th>
<th>Other</th>
<th>Overall SoE</th>
<th>Conclusion statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective surgery vs. nonoperative management</td>
<td>Death</td>
<td>3 (7288)</td>
<td>Moderate</td>
<td>Unclear&lt;supOO&lt;/sup&gt;</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Insufficient&lt;supPP&lt;/sup&gt;</td>
<td>No conclusion regarding surgery vs. no surgery. Rare events.</td>
</tr>
<tr>
<td></td>
<td>Recurrence</td>
<td>3 (7288)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>High&lt;supQQ&lt;/sup&gt;</td>
<td>Elective surgery has lower recurrence OR 0.16 (0.09, 0.27)</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay</td>
<td>2 (7179)</td>
<td>High</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>No conclusion regarding surgery vs. no surgery.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Total serious AE</td>
<td>4 (2928)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Indirect&lt;supRR&lt;/sup&gt;</td>
<td>None</td>
<td>Insufficient</td>
<td>Estimate unclear</td>
</tr>
<tr>
<td></td>
<td>30-day mortality</td>
<td>9 (199,915)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>0.7% (0.3, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Reoperation</td>
<td>6 (49,004)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Low</td>
<td>5.5% (3.1, 8.5)</td>
</tr>
<tr>
<td></td>
<td>Anastomotic leakage</td>
<td>6 (15,367)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>None</td>
<td>Low</td>
<td>4.3% (2.2, 6.9)</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>7 (82,597)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>1.6% (1.0, 2.3)</td>
</tr>
<tr>
<td></td>
<td>Site infection</td>
<td>4 (3272)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>1.4% (0.8, 1.9)</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>5 (65,459)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>0.7% (0.1, 1.6)</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td>4 (36,970)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>0.6% (0.2, 1.1)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>5 (43,818)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Precise</td>
<td>Direct</td>
<td>None</td>
<td>Moderate</td>
<td>0.3% (0.1, 0.6)</td>
</tr>
<tr>
<td>Predictors of AE</td>
<td>Various AE</td>
<td>4 (25,233)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Direct</td>
<td>Sparse</td>
<td>Insufficient</td>
<td>Estimate unclear</td>
</tr>
</tbody>
</table>

Abbreviations: AE = adverse events, DVT = deep vein thrombosis, MI = myocardial infarction, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

<supOO</sup> The two RCTs were underpowered, but the NRCS found a very large association.

<supPP</sup> Only one unadjusted NRCS provided adequate data. The two RCTs were underpowered, with one death between them. Thus the conclusions are based on a single study only.

<supQQ</sup> Although, the studies had some risk of bias, it was unlikely to be severe enough to change the conclusions of the very strong effect size.

<supRR</sup> It was unclear what was meant by total serious adverse events for several studies.
Discussion

Findings in Relation to the Decisional Dilemma(s)

Most of the clinical questions posed by this SR about nonsurgical management of patients with acute colonic diverticulitis and medical and surgical interventions to prevent recurrence remain unanswered. Much of the evidence base is sparse and many of the studies, though of at least fair methodological quality, did not address the most pertinent clinical questions or were underpowered to effectively do so.

CT Imaging

As was understood prior to our review, there is moderate SoE that CT imaging has high sensitivity and specificity to diagnose acute diverticulitis among patients presenting to the ED with clinical suspicion of diverticulitis. Since studies had to rely primarily on clinical diagnoses of diverticulitis (which included CT imaging results), the studies’ reference standard was imperfect. However, clinical examination (based on history, physical examination, and laboratory test) is poor at differentiating acute diverticulitis from other causes of abdominal pain and cannot accurately differentiate complicated from uncomplicated disease.

Nonsurgical Treatment of Acute Diverticulitis

Outpatient Management

Regarding management decisions for patients with acute diverticulitis, very few adequately conducted studies have addressed the question of the need for hospitalization of those patients with relatively mild disease or the value of interventional radiology procedures for those patients with abscesses. Although the evidence is relatively sparse and of low SoE, the evidence suggests that patients with uncomplicated disease are likely to do as well with outpatient management as hospitalization.

Antibiotics

There is low SoE that antibiotics for patients with uncomplicated diverticulitis may result in no difference in recurrence risk, quality of life, or need for surgery compared to no antibiotics. Evidence regarding other outcomes and comparing different antibiotic regimens is insufficient.

Interventional Radiology

Very few adequate studies have compared interventional radiology procedures (specifically percutaneous drainage) to usual medical care alone. Most studies that compared these approaches failed to control for the inherent differences between patients selected (and willing) to undergo abscess drainage and those who are treated medically. Ultimately, the evidence is insufficient to assess the clinical value of percutaneous drainage compared to avoiding the procedure.

Colonoscopy After an Episode of Acute Diverticulitis

There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis may, ultimately, have similar rates of CRC than those who do not undergo colonoscopy; however, no studies evaluated comparative risks of CRC death. However, there is
also low SoE that patients with recent diverticulitis may have an increased likelihood of having undiagnosed CRC or advanced colonic neoplasia (CRC or advanced adenomas).

The evidence suggests that among people with recent acute diverticulitis, those 50 or older or who had complicated diverticulitis are at increased risk of having CRC or premalignant lesions on colonoscopy. Colonoscopies after acute diverticulitis rarely have complications or incomplete tests.

Prevention of Recurrence

Nonsurgical Interventions

Among nonsurgical interventions to prevent recurrence of diverticulitis, only 5-ASA has been evaluated by more than one or two comparative studies. There is high SoE that 5-ASA does not reduce the risk of diverticulitis, and there is even a suggestion that people using 5-ASA may be at a small increased risk of recurrence. There is, though, also high SoE that 5-ASA does not cause important adverse events. Evidence pertaining to other pharmacologic interventions, including rifaximin, probiotics, and combinations of these three interventions, are sparse, each having been evaluated by only a single comparative study. Burdock tea, a diuretic and antipyretic tea commonly used in Asian medicine, has also been evaluated by a single study. Of note, no eligible studies have evaluated any medical nutrition therapies.

Elective Surgery

Among patients with either a history of complicated diverticulitis or multiple recurrent diverticulitis, there is a high SoE indicated that elective surgery resulted in much lower rates of diverticulitis recurrence than nonsurgical interventions. Serious adverse events, including 30-day mortality (at 0.7%), need for reoperation (5.5%), and anastomotic leakage (4.3%) were not uncommon. The evidence is sparse to evaluate risk of long-term death, but there is some indication that at 5 years of followup, patients who underwent elective surgery were at reduced risk of death. In addition, none of the studies evaluated psychosocial outcomes such as anxiety, stress, or fear related to the risk of recurrent episodes of acute diverticulitis.

Strengths and Limitations

With few exceptions, the evidence base examined in this SR is sparse or of low SoE. As noted, many important clinical questions have not been addressed by sufficient numbers of studies that meet basic criteria (for most questions, comparative studies with appropriate adjustment for inherent differences between compared groups). Evidence is particularly sparse for questions related to the benefits and harms of CT scanning for acute diverticulitis, the appropriateness of outpatient management of uncomplicated or mildly complicated diverticulitis, interventional radiology for nonsurgical complicated diverticulitis, and various interventions for prevention of recurrent diverticulitis. In addition, there is very limited evidence regarding which patients might benefit most from (or be most harmed by) the various interventions. The lack of evidence about heterogeneity of treatment effects (which patients would most benefit), arguably, is most important for elective surgery because, despite the strong evidence of an important clinical benefit to surgery, clearly elective surgery cannot, and probably should not, be recommended for all patients with a history of acute diverticulitis. It is of paramount importance to determine criteria to establish who would most benefit.
Only for patients undergoing colonoscopy have studies systematically addressed which patients are at highest risk of outcomes. However, while the studies have found that older patients and those with recent complicated diverticulitis are at particularly high risk of CRC and advance colonic neoplasia, the studies comparing patients with diverticulitis to the general population have not evaluated whether younger patients or those with recent uncomplicated diverticulitis, specifically, are at higher risk of CRC than patients in the general population. Also, importantly, the studies have not adequately addressed whether patients who undergo colonoscopy after diverticulitis are at decreased risk of dying from CRC compared to patients who forgo colonoscopy. Ultimately, this is the primary unanswered clinical question pertaining to colonoscopy.

From a methodological perspective, it was common that studies were underpowered (too small) to address the most important clinical outcomes, failed to address the clinically important outcomes, or were inadequately analyzed. For many of the questions pertaining to treatment dilemmas, the RCTs tended to be too small (thus, underpowered) to detect differences between treatments in important, but relatively rare, clinical outcomes (such as treatment failure, unplanned emergency surgery, and death). The RCTs mostly evaluated less clinically important outcomes. Many of the NRCSs were designed to be large enough to address at least some of the clinically important outcomes, but did not, or did not adequately, control for the inherent differences between groups. Thus, the findings of these NRCSs may have been biased toward findings that more intensive interventions are associated with worse outcomes (because the more intensive interventions were mostly used in the sicker patients who, by definition, are at highest risk of poor outcomes). Several of the colonoscopy and elective surgery studies were based on registries or administrative databases. However, these data sources are unlikely to be accurate or sufficiently granular about differences in disease severity across patients and other clinical factors such as patient comorbidities, not to mention patient preferences and life goals, which can influence the threshold for intervention (e.g., whether to undergo colonoscopy or to have elective sigmoidectomy).

We believe that our literature search was complete and did not systematically miss studies. We did not reject any study due to language restrictions or study setting (including country). It appears that the large majority of studies that were unavailable to us were conference abstracts, so we might have missed some cutting-edge studies. We restricted the evidence base to the past 30 years, based on changing diagnostic criteria for acute diverticulitis in the 1990s. We might have, thus, missed some important older studies that might still be pertinent. However, none of the stakeholders we collaborated with knew of such studies or were concerned by the choice of dates. While we restricted some study designs based on sample sizes, we do not think the smaller studies would have altered conclusions. Additional studies of the harms of elective surgery might have made our estimates more precise but are unlikely to have changed our overall conclusions that surgical complications are uncommon. Smaller comparative studies are highly unlikely to have been adequately analyzed.

We were fairly liberal about decisions to perform meta-analyses. However, where one might have reasonably chosen not to meta-analyze studies (because of clinical heterogeneity of included studies or post hoc decisionmaking), we explicitly point this out. We chose to use meta-analysis mostly as an indicator of possible effect (or of likelihood of an outcome or finding) rather than to provide precise estimates. In particular, for meta-analyses of colonoscopy findings (rates of findings) and elective surgical harms, we conducted meta-analyses to provide an indication of how common (or rare) outcomes are. For evaluations of elective surgery
complications, we acknowledge that we did not adequately account for the differences across studies of surgery or patient characteristics. However, no clear patterns were seen across studies to explain the statistically large differences in surgical complication rates.

**Applicability**

The evidence base, even where insufficient to make conclusions about intervention effect, appeared to be generally applicable to patients with either suspicion of acute diverticulitis, diagnosed acute diverticulitis, or history of diverticulitis (depending on the evaluated intervention). Most studies (at least for nonsurgical interventions) described their eligibility criteria sufficiently to determine that the included participants are those for whom the intervention is potentially appropriate. However, many studies did not provide sufficient detail to understand the detailed level of severity of disease or of potential risk factors for poor outcomes. Arguably, more importantly, as described above, studies rarely evaluated subgroups (except for studies of colonoscopy) and failed to address heterogeneity of treatment effect. Such analyses could allow a better understanding of whom the findings are most applicable to. Many of the single group studies of elective surgery (often from registries or other large databases) did not clearly describe their included patients.

The one caveat about applicability in regard to patient or disease characteristics is that the large majority of studies were conducted in “western” countries, where left-sided diverticulitis is predominant. Only four studies were from East Asia (specifically South Korea and Japan), where right-sided diverticulitis is predominant.

**Implications for Clinical Practice, Education, Research, or Health Policy**

This review was nominated by the ACP to summarize the evidence base for a planned new clinical practice guideline on management of patients with diverticulitis. This goal informed the scope of the review to primarily address the needs of nonsurgical decisionmakers and patients. Unfortunately, many of the important questions about which interventions should be used for which patients remain either unanswered or answered with only low SoE. It is likely that many specific recommendations for management will be weak suggestions based largely on expert opinion. These include important questions related to benefits and harms of CT imaging, appropriateness of outpatient management of mild acute diverticulitis, interventional radiology for complicated diverticulitis, who needs antibiotics and choice of antibiotics, whether colonoscopy is needed for patients under age 50 (particularly those with uncomplicated diverticulitis), what nonsurgical interventions are effective to reduce the risk of recurrence (and who would most benefit), and which patients should be referred for possible elective surgery to prevent recurrent diverticulitis.

**CT Imaging**

Despite the lack of a definitive reference standard to diagnose acute diverticulitis (since only a minority of patients have surgical, pathological, or colonoscopy confirmation of disease), the evidence supports the common understanding that CT imaging is accurate to diagnose acute diverticulitis. However, there is a lack of evidence to support the accuracy of CT imaging for grading severity of disease.
The clinical implications of false positive, false negative, and incidental findings remain unclear. While the studies suggest a low SoE that misdiagnoses on CT did not result in poor clinical outcomes, the studies were relatively few and small and did not adequately address what good outcomes were clearly a result of findings on CT or what bad outcomes (including unnecessary interventions and their harms) occurred as a result of errors on CT. The evidence is insufficient regarding the test accuracy of clinical staging classifications based on CT imaging. In particular, no studies evaluated test accuracy of staging systems commonly used in the U.S.

While a small number of studies found that incidental findings were common among patients undergoing CT for acute abdomen, the clinical significance of the findings (either beneficial or harmful) was not adequately evaluated.

Nonsurgical Treatment of Acute Diverticulitis

Outpatient Management

For selected patients with uncomplicated diverticulitis (or mild complicated diverticulitis) whose pain and other symptoms can be controlled in the ED, outpatient treatment leads to clinical outcomes that are no worse than inpatient treatment. Poor clinical outcomes, including the need for emergency surgery, were uncommon in this group of patients, suggesting that most patients do relatively well, regardless of whether they recover in-hospital or at home. Even long-term outcomes appear to be similar in those treated for their acute diverticulitis either inpatient or outpatient.

Antibiotics

It appears that avoidance of antibiotics for patients with uncomplicated acute diverticulitis may be safe for the large majority of patients. However, this conclusion is largely based on the fact that complications, including death, emergency surgery, diverticulitis-related complications, and treatment failure are rare events for these patients. Because of the low rate of these adverse outcomes, estimates of effects are highly imprecise. There is, though, low SoE that recurrence rates, quality of life, and long-term elective surgery rates are similar regardless of use of antibiotics. For patients who do receive antibiotics, the evidence is insufficient to guide choice of antibiotic regimen. Each study evaluated a unique pair of antibiotic regimens that differed in choice of antibiotics, route, and duration of treatment.

Interventional Radiology

The evidence base provides sparse evidence to guide the decision whether to use percutaneous drainage or other interventional radiology procedures for patients with acute complicated diverticulitis.

Colonoscopy After an Episode of Acute Diverticulitis

For patients treated for acute diverticulitis who do not undergo emergency surgery (such as sigmoidectomy), an important clinical consideration is whether they should have a colonoscopy to rule out CRC or high-risk lesions that might have played a role in the development of the acute diverticulitis. There is concern that these patients might be at increased risk for having colon neoplasias (whether related to their having diverticulitis or to possible misdiagnosis of inflamed CRC as acute diverticulitis). While three studies provide low SoE that rates of ultimate diagnoses of CRC are similar among those who undergo colonoscopy as part of their post-
diverticulitis care and those who do not, none of the studies address the most important clinical question of whether having a colonoscopy affects the risk of death from CRC. Overall, patients with a recent episode of acute diverticulitis (who undergo colonoscopy) are likely at increased risk of having CRC compared with the general population of individuals undergoing routine colonoscopy screening. However, it is unclear to what extent this difference is related to differences among those who choose to undergo colonoscopy (e.g., because of a family history of CRC or gastrointestinal symptoms, such as rectal bleeding) and those who decline colonoscopy. One large registry study from Denmark evaluated the association between a history of diverticulitis and a history of CRC, finding a strong association; however, the study did not assess the relative clinical value of colonoscopy soon after an episode of diverticulitis. Nevertheless, the study did find that most new diagnoses of CRC (after diverticulitis) occurred within 500 days of the diverticulitis hospitalization. The study also suggested that those patients who undergo colonoscopy (with or without a history of diverticulitis) are more likely to have CRC, strongly suggesting that people are undergoing colonoscopy based on risk factors for CRC beyond diverticulitis alone.

CRC and high-risk lesions are relatively common among patients with recent acute diverticulitis. About 2 percent have been found to have CRC (moderate SoE), 7 percent advanced colonic neoplasia (CRC or advanced adenoma; moderate SoE), and up to 3 percent have each of advanced adenoma, adenomas with high-grade dysplasia, or large adenomas. Incomplete (or failed) colonoscopies are uncommon in this population and procedure-related complications are rare. The evidence base is internationally very diverse, with only one study each from the U.S. or Canada; however, there were no clear patterns in CRC rates across countries (or continents). While there may be concerns about risks of complications or failed colonoscopies soon after bouts of acute diverticulitis, the evidence does not support that these are common events. Notably, none of 878 patients who underwent colonoscopy had a complication (e.g., major bleeding or perforation). As a point of reference, a 2017 systematic review found that across 39 studies (mostly from the U.S. or Europe), the pooled risk of major bleeding was , the pooled overall risk of major bleeding after colonoscopy was 0.08 percent (95% CI 0.018 to 0.163) and the overall risk of perforation was 0.007 percent (95% CI 0.0006 to 0.017).

However, most patients with diverticulitis are over age 50. The current guidance from multiple societies is for (essentially) all people in this age group to undergo colonoscopy. Consistent with this recommendation, there is moderate SoE that older (≥50 years) patients with diverticulitis are at about 3-times increased risk of CRC than younger patients and high SoE that they are at about 8-times increased risk of advanced colonic neoplasia. Although across all studies, we do not have a clear indication of the risk of CRC among younger (<50 years) patients, in three of the four studies that compared age subgroups, no one under age 50 was found to have CRC. In addition to older age, recent complicated (versus uncomplicated) diverticulitis has been shown to be a strong risk factor for abnormal colorectal findings on colonoscopy. There is high SoE that patients with complicated diverticulitis have almost 6-times increased risk of CRC and 3-times increased risk of advanced colonic neoplasia.

**Prevention of Recurrence**

**Nonsurgical Interventions**

Despite its apparent safety, the evidence strongly supports (with high SoE) that 5-ASA is not effective to reduce the risk of recurrent diverticulitis. There is even a suggestion that people
using 5-ASA may be at a small *increased* risk of recurrence. Although several other nonsurgical interventions have been evaluated in comparative studies, each has been evaluated by only a single study; thus, the evidence base does not support any conclusions regarding their effectiveness. Although of particular interest to patients and clinicians, medical nutrition therapies have not been evaluated by comparative studies.

**Elective Surgery**

An important consideration for patients with a history of acute diverticulitis is whether to undergo elective sigmoidectomy or colectomy with the goal of preventing recurrent episodes and the possible need for emergency surgery and a colostomy. Surgery studies have evaluated patients with either a history of complicated diverticulitis or multiple recurrent diverticulitis, those patients most likely to be offered elective surgery. Among these patients, studies consistently found a large benefit for elective surgery in terms of prevention of recurrent diverticulitis. However, none of the studies addressed which patients may benefit more (or less) from elective surgery. Notably, serious adverse events, were not uncommon.

**Future Research**

There is a clear need for high-quality research to address all these issues. Ideally, large-scale, multicenter RCTs should be conducted in unrestricted populations (i.e., without eligibility restrictions that may reduce applicability) with appropriate subgroup analyses. RCTs should be large enough to evaluate potential clinically important differences in rates of the most important outcomes to patients (e.g., death, treatment failure, emergency surgery, and time to recurrence) and important harms, adverse events, and complications (e.g., risk of C diff infection from antibiotics, which can be devastating for patients who already have diverticulitis; postoperative death; and permanent stomas).

Alternatively, large databases should be adequately analyzed to compare interventions. It is our strong belief that no (or rare) future studies should be considered that compare groups of patients who are inherently different without adequate adjustment for these differences. Unadjusted comparisons of, for example, hospitalized versus discharged patients or those who undergo or do not undergo percutaneous drainage of abscesses, can generally only conclude that sicker patients (who are, for example, more likely to be hospitalized or to undergo percutaneous drainage) fare worse. Ideally, propensity score analysis (or similar techniques) should be used. These analyses estimate the likelihood that each patient had one or the other intervention and control for this likelihood. These analyses generally require relatively large numbers of patients for whom there is granular data about their risk factors for outcomes.

Furthermore, future studies should emphasize evaluations of heterogeneity of treatment effect to better understand which patients may most benefit from (or may be most harmed by) a given intervention. This can be done relatively simply with subgroup analyses, but more sophisticated evaluations may be appropriate. As for the NRCSs, it is important that the subgroup comparisons be adequately adjusted. For example, in a given set of patients, those with complicated diverticulitis may be fundamentally different from those with uncomplicated disease (beyond the presence or absence of abscesses).

**Conclusions**

Many questions remain inadequately answered regarding the best management of patients with acute diverticulitis or to prevent future recurrences. Prior reviews have demonstrated that
CT imaging accurately diagnoses acute diverticulitis. For selected patients, outpatient management may be as effective as inpatient care. For patients with acute uncomplicated diverticulitis, it may be safe and appropriate to forgo antibiotics. The evidence base is inconclusive, though, about choice of antibiotic regimen for patients with complicated diverticulitis. The evidence is insufficient to assess the clinical value of percutaneous drainage. Patients with recent episodes of diverticulitis are at risk of having undiagnosed CRC or advanced colonic neoplasia, particularly if they are at least 50 years of age or have had complicated diverticulitis. The use of 5-ASA does not reduce (and may increase) the risk of recurrence of diverticulitis but is not more harmful than placebo. Patients who undergo elective surgery are at greatly reduced risk of recurrent diverticulitis; serious surgery-related adverse events are uncommon. However, for elective surgery in particular, and for all other evaluated interventions, the evidence does not adequately address which patients would benefit most from a given intervention. There is a compelling need for future, well-conducted studies that address both effectiveness (and harms) of interventions and heterogeneity of treatment effect.
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