Antibiotics Versus No Antibiotics for Acute Uncomplicated Diverticulitis: A Systematic Review and Meta-Analysis

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BACKGROUND: Antibiotics are routinely used for diverticulitis irrespective of severity. Current practice guidelines favor against the use of antibiotics for acute uncomplicated diverticulitis.

OBJECTIVE: We performed a systematic review and meta-analysis to examine the role of antibiotic use in an episode of uncomplicated diverticulitis.

DATA SOURCES: PubMed/Medline, Embase, Scopus, and Cochrane were used.

STUDY SELECTION: Eligible studies included those with patients with uncomplicated diverticulitis receiving any antibiotics compared with patients not receiving any antibiotics (or observed alone).

MAIN OUTCOME MEASURES: Pooled odds rate of total complications, treatment failure, recurrent diverticulitis, readmission rate, sigmoid resection, mortality rate, and length of stay were measured.

RESULTS: Of 1050 citations reviewed, 7 studies were eligible for the analysis. There were total of 2241 patients: 895 received antibiotics (mean age = 59.1 y; 38% men) and 1346 did not receive antibiotics (mean age = 59.4 y; 37% men). Antibiotics were later added in 2.7% patients who initially were observed off antibiotics. Length of hospital stay was not significantly different among either group (no antibiotics = 3.1 d vs antibiotics = 4.5 d; $p = 0.20$). Pooled rate of recurrent diverticulitis was not significantly different among both groups (pooled OR = 1.27 (95%, CI 0.90–1.79); $p = 0.18$). Rate of total complications (pooled OR = 1.99 (95% CI, 0.66–6.01); $p = 0.22$), treatment failure (pooled OR = 0.68 (95% CI, 0.42–1.09); $p = 0.11$), readmissions (pooled OR = 0.75 (95% CI, 0.44–1.30); $p = 0.31$). and patients who required sigmoid resection (pooled OR = 3.37 (95% CI, 0.65–17.34); $p = 0.15$) were not significantly different among patients who received antibiotics and those who did not. Mortality rates were 4 of 1310 (no-antibiotic group) versus 4 of 863 (antibiotic group).

LIMITATIONS: Only 2 randomized controlled studies were available and there was high heterogeneity in existing data.

CONCLUSIONS: This meta-analysis of current literature shows that patients with uncomplicated diverticulitis can be monitored off antibiotics.

KEY WORDS: Antibiotics; Diverticulitis.

Symptomatic diverticulosis or diverticular disease of the colon is the fifth most common GI disease in terms of direct and indirect healthcare costs in Western countries, with similar frequency in men and women.[1–3] Diverticular disease as a clinical entity can present as diverticular bleeding, acute or chronic diverticulitis, uncomplicated diverticulosis with symptoms such as lower abdominal pain and constipation, and infrequently

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segmental colitis associated with diverticulosis. The prevalence and annual incidence of diverticular disease in the United States are ≈2.5 million and 300,000.[4] Approximately 10% to 25% of those with diverticulosis will experience symptomatic disease, and 15% to 20% of those with symptomatic disease are diagnosed with acute diverticulitis.[1,5,6] The lifetime risk of acute diverticulitis in patients with diverticulosis ranges from 4% to 25% and it is on the rise, in part because of the ageing population.[7,8]

Acute diverticulitis is the most common cause of hospitalization from diverticulosis.[9] Most patients experiencing an acute diverticulitis attack have an *acute uncomplicated diverticulitis* (AUD), defined by the absence of bowel perforation, abscess/phlegmon, fistula, or bleeding. Previous literature suggests a high risk of recurrence and subsequent complications from acute diverticulitis. However, recent series suggest that the natural history of sigmoid diverticulitis, which is the most common site of diverticulitis, is more benign.[10] The overall recurrence rate of diverticulitis is reported in literature as ≈13% to 19%, and a minority develop complications (<5%).[6,11] Moreover, most perforations do not occur after recurrences but after the first attack of acute diverticulitis. Multiple recurrences were not associated with a higher chance of mortality, nor did they lead to a higher rate of complicated disease. The main cost driver is the use of hospital facilities (bed days), which accounts for 65% to 70% of the total health care costs associated with diverticulitis.[1,6]

The administration of antibiotics has long been the cornerstone of treatment of AUD, and most patients get admitted to the hospital for the initiation of intravenous antibiotics. Contrary to current American Gastroenterology Association practice, guidelines that recommend antibiotics should be used selectively rather than routinely in patients with AUD.[12] The evidence for this recommendation is of low quality. Recent studies, including 2 randomized controlled trials (RCTs),[13,14] have questioned the necessity of the use of antibiotics for AUD. Routine nonselective use of antibiotics impacts the health care cost on a global level and increases adverse effects related to medications and unnecessary hospital stay. No previous meta-analysis has been attempted in a large cohort of patients to assess outcomes in patients with AUD who were given antibiotics compared with those who were observed without antibiotics.

We performed a systematic review and meta-analysis of current literature to assess the role of antibiotics in patients with AUD compared with observation without antibiotics with a focus on a decrease in the rate of recurrent diverticulitis and other important complications.

MATERIALS AND METHODS

This systematic review and meta-analysis has been performed according to Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[15] Figure 1 demonstrates the process for final study selection.

Search Strategy

A comprehensive electronic literature search was conducted in PubMed/Medline, Embase, Scopus, and Cochrane databases to identify studies that assessed the role of antibiotics for AUD compared with conservative care or observation alone (no-antibiotics group) from the beginning of indexing for each database to December 31, 2017. Bibliographic review of selected articles and major GI proceedings were examined as secondary sources for full-length articles of studies of antibiotic use for AUD compared with no antibiotics. A literature search was performed and verified by 2 independent authors (M.D. and J.F.), with no restriction in language. The search for studies of relevance was performed using the following text words and corresponding Medical Subject Heading/Emtree terms: *diverticulitis* (or *diverticular disease*) and *antibiotics* and/or *management*.

Eligibility Criteria

Two reviewers (M.D. and J.F.) independently evaluated all of the studies retrieved according to the eligibility criteria, and any disagreement was resolved by consensus. Studies were included if they met all of the following criteria: RCTs or retrospective studies with a control group comparing the use of antibiotics versus no antibiotics (monitoring only) in the management of AUD and a study reporting outcomes of interest (total complications, treatment failure, length of hospitalization, recurrent diverticulitis, sigmoid resection, and mortality rate) among both groups. Studies where there was no control arm (monitoring alone or no-antibiotics group), case reports/series, editorials, review articles, and studies not providing outcomes of interest were excluded. Studies of patients with severe or complicated diverticulitis (perforation, fistula, or abscess formation) were excluded.

Data Extraction and Quality Assessment

Data were extracted independently and verified for accuracy by the other reviewer (V.N.). Any disagreement was resolved by consensus. The following data were extracted from each study: first author, year of publication, study design, number of participants, age, sex, information on participants in each group, leukocyte count (white blood cells), and C-reactive protein on admission, follow-up duration, rates of total complications, treatment failure, length of hospitalization, recurrent episodes of diverticulitis, patients undergoing or requiring sigmoid resection, readmission rates, and mortality rates among both group of subjects. We collected data as numbers from individual studies or frequency of events (percentage) or effect esti-

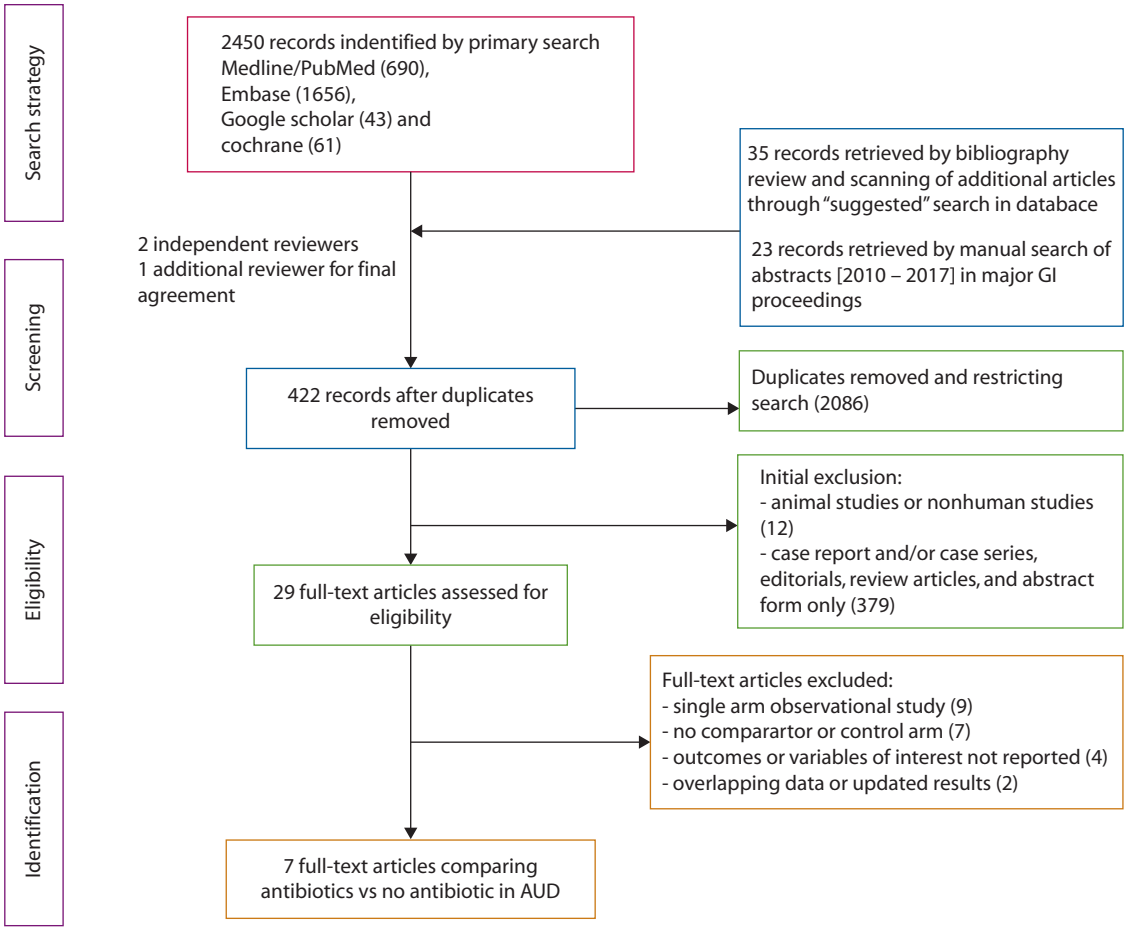

FIGURE 1. Study flow diagram depicting search strategy, inclusion, eligibility, screening, and identification of final studies for analysis. AUD = acute uncomplicated diverticulitis.

mates with 95% CI and adjustments. Total complications were inclusive of perforation, obstruction, fistula, abscess, or stricture. *Treatment failure* was defined among studies as the addition of antibiotics among the no-antibiotics group or persistence of symptoms or need for emergent surgery in those treated with or without antibiotics. Study quality was assessed using Newcastle–Ottawa scale (score ≥7 considered high quality; see Table S1, Supplemental Digital Content 1, http://links.lww.com/DCR/A877).[16]

Outcomes

We collected information on demographic variables from both groups of patients and tabulated this information for comparison of these demographic variables among both groups, including length of hospital stay and mortality rates. The primary outcome of the study was pooled rates of recurrent diverticulitis among groups with antibiotics versus conservative management alone (no antibiotics). Secondary outcomes were pooled rates of total complications, treatment failure, readmission, and sigmoid resection rates. Numbers needed to treat (NNT) was calculated as well, including NNT with antibiotics to prevent another episode of diverticulitis in AUD and to prevent any complication in AUD. We performed sensitivity analysis by only incorporating RCTs to derive pooled rates of recurrent diverticulitis, total complications, and treatment failure.

Statistical Analysis

The measure of effect of interest was the OR, an estimate of high chances of detection of intervention compared with control. The primary outcome of interest, pooled rate of recurrent diverticulitis, was calculated with 95% CIs with a random-effects model if heterogeneity was identified. Similarly, pooled ORs (95% CI) with corresponding *p* values were calculated for secondary outcomes. Corresponding forest plots were constructed for pooled estimates of these outcomes, and weights of individual studies are represented by the size of individual squares. All of the meta-analytic computations, including the pooled estimates and 95% CIs for pooled rates, and NNT, as well as the measurement of heterogeneity (measured as I^2 statistics), were performed using statistical software Review Manager version 5.3 (Cochrane Community, London, United Kingdom).

Student *t* test was used to assess any significance of difference between length of stay between the 2 groups. This was not a meta-analytical outcome or test, and Microsoft Excel (Microsoft, Redmond, WA) was used for this calculation. I^2 values of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% were indicated as low, moderate, substantial, and considerable heterogeneity. $P < 0.05$ was considered statistically significant for all outcomes. Publication bias was derived to assess for the role of any specific studies responsible using Cochrane guidelines and Review Manager software in the form of a funnel plot.

RESULTS

Study Characteristics

Literature review yielded a total of 2508 records (Fig. 1). After removing duplicates, there were 422 records that underwent additional screening for eligibility. Of this, 29 full-text articles were reviewed, and there were total of 7 studies that were eligible for the analysis.[13,14,17–21] There were 2 RCTs,[13,14] and 5 were observational cohort or retrospective studies.[17–21] There were total of 2241 patients, of whom 895 received antibiotics, whereas 1346 did not receive antibiotics for treatment of AUD. Patients in the antibiotics group had an average age of 59.1 years, and 38% were men. Patients in the no-antibiotics group had an average age of 59.4 years, and 37% were men. Average follow-up among inclusion studies ranged from 6 to 30 months. Antibiotics were later added in 25 (2.7%) of 906 patients who initially were observed off antibiotics. Patients who received antibiotics stayed in the hospital longer compared with those who did not (4.5 vs 3.1 d); however, length of hospital stay was not significantly different among either group ($p = 0.20$). Mortality rate was slightly lower among patients who did not receive antibiotics compared with those did but was not statistically different (0.3% (4/1346) vs 0.5% (4/895); $p = 0.39$).

Study quality assessment was performed using the Newcastle–Ottawa scale and is shown in Table S1 (Supplemental Digital Content 1, http://links.lww.com/DCR/A877). Study and patient characteristics are shown in Table 1. Inclusion and exclusion criteria of inclusion studies and outcomes among individual studies are shown in Tables S2 and S3, available at Supplemental Digital Content 1, http://links.lww.com/DCR/A877.

Primary Outcome

Six studies provide information regarding recurrent diverticulitis. The pooled rate of recurrent diverticulitis was slightly higher among patients who received antibiotics compared with those who did not (12.6% vs 11.5%). However, on pooled analysis of estimates of recurrent diverticulitis, there was no statistically significant difference between those who received antibiotics and those who did

TABLE 1. Study and patient characteristics among control group (no antibiotics) and those who received antibiotics for AUD among inclusion studies

Study	*Type of study*		*Age, y*	*Men, n*	*Women, n*	*WBC on admission (×10⁹ cells per liter)*	*CRP on admission, mg/L*	*Follow-up (mean or median)*
Chabok et al[13]	RCT	No antibiotics (n = 309)	57.1 (13.2)	110	199	12.3 (3.3)	91 (61)	12 mo
		Antibiotics(n = 314)	57.4 (12.8)	110	204	12.6 (3.1)	100 (62)	
		p	0.853	0.882	0.882	0.276	0.070	
Hjern et al[20]	Retrospective	No antibiotics (n = 193)	59	67 (35%)	126 (65%)	10.2	87	30 mo
		Antibiotics(n = 118)	60	44 (37%)	74 (63%)	11.7	119	
		p	0.45	0.65	0.65	<0.001	<0.01	
Daniels et al[14]	RCT	No antibiotics (n = 262)	57.4 (48.5–64.6)	135	127	12.5	73	6 mo
		Antibiotics(n = 266)	56.3 (48.5–63.8)	132	134	12	82.7	
Brochmann et al[17]	Retrospective cohort study	No antibiotics (n = 177)	60.3 (13.01)	58	119	10.5 (3)	93 (54)	12 mo
		Antibiotics(n = 47)	59.6 (13.04)	15	32	12.1 (3.2)	116 (70)	
		p	0.755	0.288	0.288	0.002	0.038	
Isacson et al[21]	Retrospective population-based cohort study	No antibiotics (n = 178)	60 (14)	68 (38%)	110 (62%)	11 (3)	85 (57)	12 mo
		Antibiotics(n = 17)	60 (17)	9 (53%)	8 (47%)	13 (3)	115 (109)	
		p	0.721	0.3	0.3	0.005	0.065	
de Korte et al[18]	Retrospective case–control study	No antibiotics (n = 191)	61 (27–92)	56	135 (71%)	12.4	99	50 mo
		Antibiotics (n = 81)	63 (34–94)	29	52 (64%)	12.9	109	
		p	0.37	0.291	0.291	0.482	0.395	
Estrada Ferrer et al[19]	Retrospective	For the group (n = 77)	57.2 (29–80)	44	33	NA	NA	6 mo

AUD = acute uncomplicated diverticulitis; WBC = white blood cell count; CRP = C-reactive protein; RCT = randomized controlled trial; NA = not applicable.

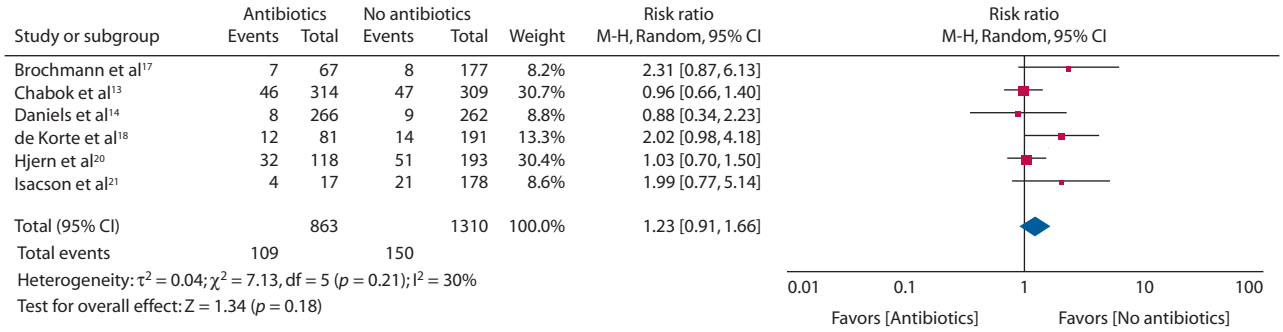

FIGURE 2. Forest plot of inclusion studies of recurrent diverticulitis among both groups. M-H = Mantel-Haenszel; df = degrees of freedom.

not ($p = 0.18$). Pooled OR was 1.27 (95% CI, 0.90–1.79). There was low heterogeneity in the inclusion studies, with I^2 of 30%. The forest plot of pooled rates of recurrent diverticulitis is shown in Figure 2.

Secondary Outcomes

The pooled rate of total complications was higher among patients who had antibiotics compared with those who were monitored off antibiotics (27.8% vs 19.8%), but there was no statistical difference between these 2 groups in pooled analysis ($p = 0.22$). Pooled OR was 1.99 (95% CI, 0.66–6.01; Fig. 3). Similarly, treatment failure (antibiotics vs no antibiotics: 3.0% vs 4.5%; pooled OR = 0.68 (95% CI, 0.42–1.09); $p = 0.11$) and readmission rates (antibiotics vs no antibiotics: 14.5% vs 15.2%; pooled OR = 0.75 (95% CI, 0.44–1.30); $I^2 = 41\%$; $p = 0.31$) were not significantly different among both groups. The rate of sigmoid resection was lower among patients who were managed conservatively (antibiotics vs no antibiotics: 4.8% vs 1.5%, pooled OR = 3.37 (95% CI, 0.65–17.34); $p = 0.15$), but there was no statistically significant difference. The forest plot of pooled rates of these outcomes is shown in Figure 4. The NNT with antibiotics to prevent another episode of diverticulitis was 50, whereas NNT with antibiotics to prevent a complication related to having AUD was 100.

Sensitivity Analysis

We performed sensitivity analysis by only incorporating RCTs to derive pooled rates of recurrent diverticulitis, total complications, and treatment failure. When analysis was restricted to high-quality evidence including RCTs (n = 2), pooled rate of recurrent diverticulitis was not found to be statistically different among patients who received antibiotics versus those who did not. The pooled rate of recurrent diverticulitis had a pooled OR of 0.94 (95% CI, 0.63–1.41; $p = 0.77$). Similarly, the pooled rates of total complications (pooled OR = 0.58 (95% CI, 0.28–1.21); $p = 0.15$) and treatment failure (pooled OR = 0.48 (95% CI, 0.21–1.09); $p = 0.08$) were not significantly different among high-quality studies of groups with antibiotics versus no antibiotics in AUD.

Publication Bias

A funnel plot (Figure S1, available at Supplemental Digital Content 1, http://links.lww.com/DCR/A877) of inclusion studies of primary outcome showed that there was no major bias, because no study was found out of the funnel. However, there were only 6 studies limiting additional examination for any significant source of bias.

DISCUSSION

This meta-analysis of ≈2200 patients shows that there was no significant difference in important clinical outcomes when antibiotics were not used in subjects with AUD compared with those who received antibiotics. This statistical nondifference did not change when analysis was restricted to RCTs alone. In addition, readmission rates and sigmoid resection rates were not significantly different, inferring

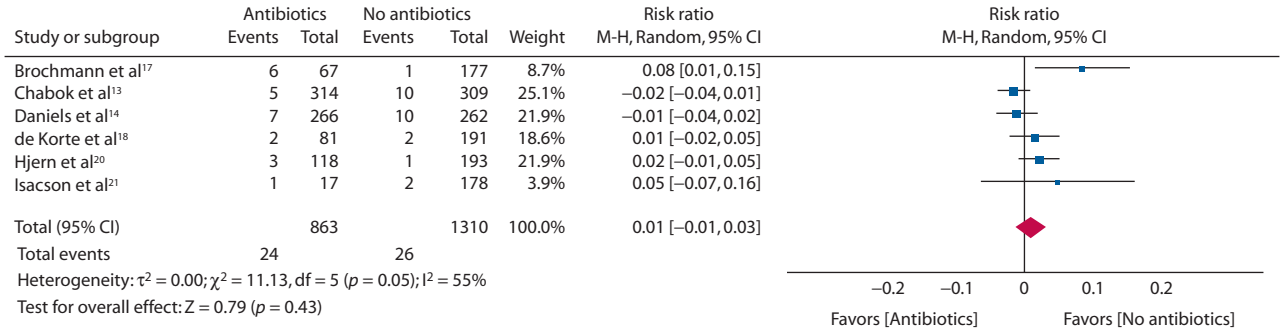

FIGURE 3. Forest plot of inclusion studies of total complications among both groups. M-H = Mantel-Haenszel; df = degrees of freedom.

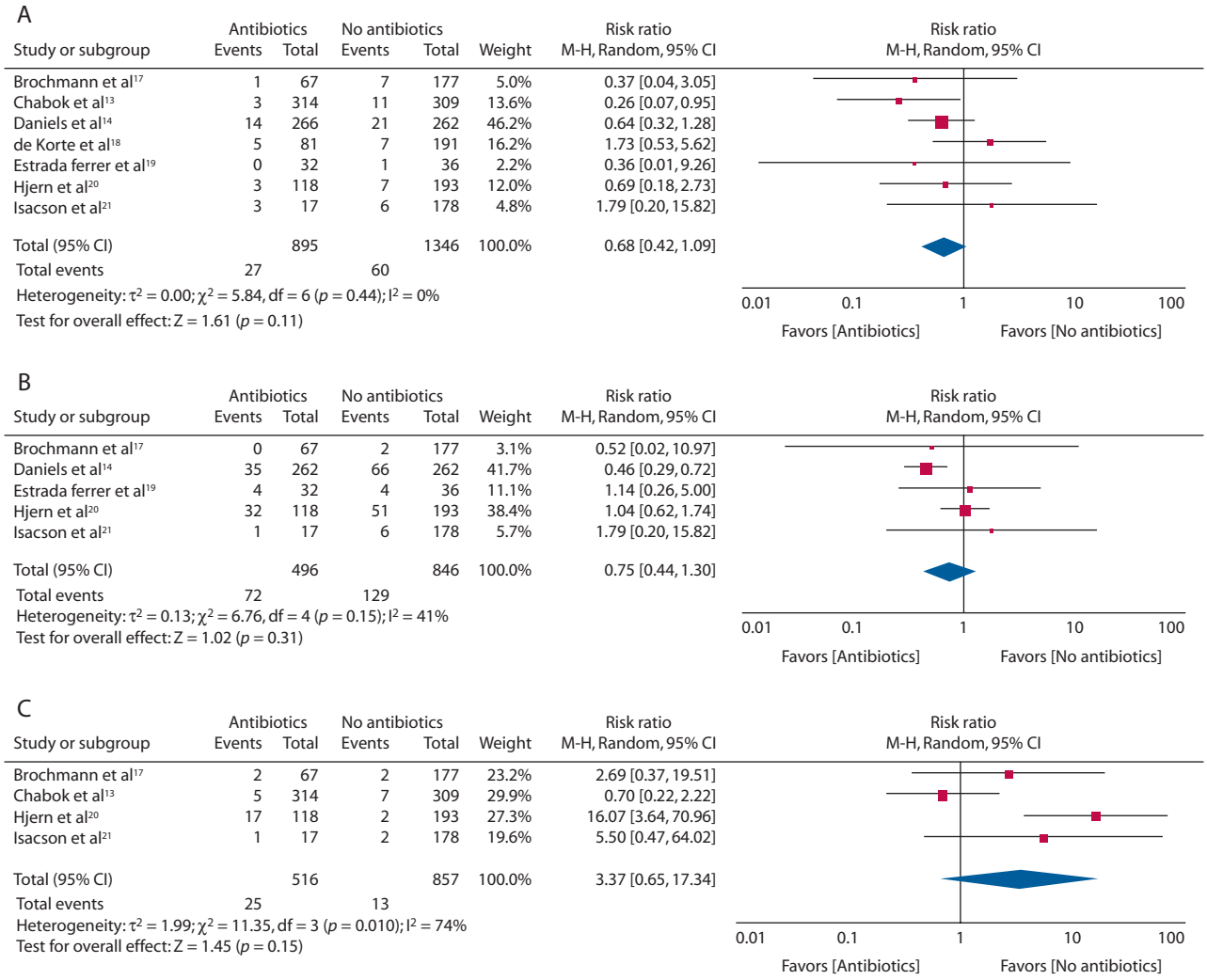

FIGURE 4. Forest plot of inclusion studies of treatment failure rates (A), readmission rates (B), and sigmoid resection rates (C) among both groups. M-H = Mantel-Haenszel; df = degrees of freedom.

that patients can be observed in a monitored setting off of antibiotics comfortably. There was low heterogeneity among included studies (≈30%–40%), suggesting low clinical or methodologic heterogeneity in pooled analysis. Because of the emerging belief that AUD may be inflammatory, to avoid complications stemming from the significant increase in antibiotics resistance, and to avoid their adverse effects, the American Gastroenterological Association has changed guidelines from routine use of antibiotics to selective use for treatment of AUD.[12] However, the rating behind the evidence was low, especially that the use of antibiotics in the treatment of AUD is based on tradition and expert opinion. This pooled analysis provides strong evidence in favor of not using antibiotics for AUD and will strengthen the current guidelines.

In clinical practice, various classification systems[22–26] are in use to guide management with an emphasis on imaging currently that also helps with identifying complicated disease early.[27] Most cases of AUD are still treated with antibiotics despite recent studies showing no difference in recovery or complications between patients treated with or without antibiotics.[13,14] Treatment without antibiotics is controversial despite evidence from several observational studies and 2 RCTs indicating that antibiotics have no benefit.[13,14,17,20,21] Antibiotics are theoretically used to target peritoneal contamination from colonic bacterial translocation or fecal spillage, although no studies to date have elucidated the microbiology of AUD. Recent literature suggests targeting the inflammatory pathophysiology of diverticulitis rather than treating with antibiotics.[28,29] The reasoning behind continued antibiotic use for AUD stems from the possibility of recurrence and complications. Another factor of routine antibiotic use is the practice of avoiding complications and fear of observation practice among practicing clinicians.

Antibiotics were later added in 25 (2.7%) of 906 patients who were initially observed off antibiotics in our meta-analysis. The reasons are not entirely clear and are

not mentioned among all of the inclusion studies. It is not clear whether this was solely because of the development of severe disease or a complication. Reasons for the addition of antibiotics in these patients could be manifold, including a lack of clinical improvement as expected and choice of health care provider involved per subjective preference. It remains unclear whether there was failure in 2.7% of the conservatively managed patients and there is a lack of available data on which reason antibiotics were prescribed. On the other hand, a majority (97%) did not require the addition of antibiotics in the control arm and were managed without it. This is another supporting outcome that should be carefully looked at in future studies. Patients who were not treated with antibiotics had a significantly lower median hospital stay than those who were treated. This shows that treating AUD conservatively can lessen the financial health care burden, accompanied with no increase in complications or treatment failure. The huge health care burden of the treatment of AUD with the development of antimicrobial therapy resistance and the adverse effects of antibiotics prompt us to consider conservative management as the optimal treatment for AUD to use the limited health care resources efficiently. The use of a more conservative approach for AUD will decrease the health care expenditure and minimize unnecessary interventions.

This meta-analysis has limitations. There were only 2 RCTs, and the rest were observational studies. However, we performed analysis restricting to high-quality studies (RCTs), and it did not change results. Another issue was methodologic heterogeneity among inclusion studies because of design and framework. In clinical practice, few patients who present to the hospital are already on oral antibiotics from primary care, and then they are placed on intravenous antibiotics irrespective of complication or worsening disease. Inclusion studies are not homogenous with regard to previous antibiotic use, and several other factors listed earlier affect the generalizability of these pooled outcomes.

CONCLUSION

Acute diverticulitis is a debilitating complication of diverticular disease that affects ≈2.5 million individuals in the United States.[4] Most cases of diverticulitis are uncomplicated, and the use of antibiotics has not been shown to prevent complications or recurrences. In the presence of evidence against the routine use of antibiotics and in light of the increased health care expenditure and the rise of antibiotic resistance, the conservative treatment of AUD with no antibiotics should be the standard of care. This systematic review and meta-analysis of published studies to date provides strong evidence against the routine use of antibiotics for AUD.

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