Antibiotics Do Not Reduce Length of Hospital Stay for Uncomplicated Diverticulitis in a Pragmatic Double-Blind Randomized Trial

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BACKGROUND & AIMS: **Antibiotic treatment is the standard care for patients with uncomplicated acute diverticulitis. However, this practice is based on low-level evidence and has been challenged by findings from 2 randomized trials, which did not include a placebo group. We investigated the non-inferiority of placebo vs antibiotic treatment for the management of uncomplicated acute diverticulitis.**

METHODS: **In the selective treatment with antibiotics for non-complicated diverticulitis study, 180 patients hospitalized for uncomplicated acute diverticulitis (determined by computed tomography, Hinchey 1a grade) from New Zealand and Australia were randomly assigned to groups given antibiotics (n = 85) or placebo (n = 95) for 7 days. We collected demographic, clinical, and laboratory data and answers to questionnaires completed every 12 hrs for the first 48 hrs and then daily until hospital discharge. The primary endpoint was length of hospital stay; secondary endpoints included occurrence of adverse events, readmission to the hospital, procedural intervention, change in serum markers of inflammation, and patient-reported pain scores at 12 and 24 hrs.**

RESULTS: **There was no significant difference in median time of hospital stay between the antibiotic group (40.0 hrs; 95% CI, 24.4–57.6 hrs) and the placebo group (45.8 hrs; 95% CI, 26.5–60.2 hrs) ($P = .2$). There were no significant differences between groups in adverse events (12% for both groups; $P = 1.0$), readmission to the hospital within 1 week (1% for the placebo group vs 6% for the antibiotic group; $P = .1$), and readmission to the hospital within 30 days (11% for the placebo group vs 6% for the antibiotic group; $P = .3$).**

CONCLUSIONS: **Foregoing antibiotic treatment did not prolong length of hospital admission. This result provides strong evidence for omission of antibiotics for selected patients with uncomplicated acute diverticulitis. ACTRN: 12615000249550.**

Keywords: STAND Study; Comparison; Cefuroxime; Amoxicillin.

Abbreviations used in this paper: **CI, confidence interval; CT, computed tomography; DMC, data monitoring committee.**

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Most current article

Diverticulosis is likely to be present in more than two-thirds of those over 80 years of age and results in symptoms in 20% of those affected.[1] Acute diverticulitis is one of the most common indications for hospital admission under general surgery, and admissions for acute diverticulitis are rising both internationally[2–4] and within New Zealand.[5]

Antibiotics have historically been a cornerstone in the management of acute diverticulitis.[6] Studies of the microbiology of acute diverticulitis have focused on those with peritonitis requiring procedural intervention[7] and extrapolated to patients with uncomplicated disease. To date, no studies have been published on the microbiology of uncomplicated acute diverticulitis. The practice of routine antibiotic therapy in the treatment of uncomplicated acute diverticulitis is thus based on low-level evidence.[1]

Over the past decade, there has been a trend toward more conservative management of uncomplicated acute diverticulitis, with studies supporting outpatient management,[8,9] questioning the need for intravenous[10] or indeed any[11–14] antibiotics. Two randomized controlled trials of antibiotics vs no antibiotics in uncomplicated acute diverticulitis demonstrated noninferiority, but these trials were not placebo-controlled.[11,12]

What You Need to Know

Background

Antibiotic treatment is regarded as standard care in management of uncomplicated acute diverticulitis. This has been challenged by 2 randomized trials, which were not placebo-controlled.

Findings

Foregoing antibiotic treatment did not prolong length of hospital admission in an international (New Zealand and Australia), multicenter, placebo-controlled, double-blinded, randomized trial.

Implications for patient care

These findings contribute to the increasing evidence to support omission of antibiotics in management of select patients with uncomplicated acute diverticulitis.

Materials and Methods

The STAND (Selective Treatment with Antibiotics for Non-complicated Diverticulitis) study was an international (New Zealand and Australia), multicenter (4 site), placebo-controlled double-blinded randomized control trial, comparing standard antibiotic therapy with placebo in the treatment of computated tomography (CT)–proven Hinchey 1a uncomplicated acute diverticulitis. The trial was pragmatically designed, in consultation with general surgeons, radiologists, emergency medicine, and infectious diseases physicians.

The primary outcome for this study was the length of hospital admission in hours from registration in the emergency department to discharge into the community. The secondary outcomes of this study were participant dropout or withdrawal rate, occurrence of adverse events, readmission within 1 week and 30 days, procedural intervention, change in serum markers of inflammation, and patient-reported pain score at 12 and 24 hours.

Ethics approval was obtained from the Ministry of Health National Ethics Committee (15/NTA/65) and Auckland District Health Board's Research Review Committee (A+5600) before trial commencement. Ethics approval for Westmead Hospital was obtained separately (HREC/16/WMEAD/186, SSA Ref: SSA/16/WMEAD/379). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry on March 18, 2015 (Australian clinical trials registration number: 12615000249550). All authors had access to the study data and reviewed and approved the final manuscript.

Participants were recruited from 3 New Zealand hospitals (Auckland City [December 2015 to March 2019], Middlemore [July 2016 to July 2017], and North Shore [April 2016 to May 2019]) and 1 Australian hospital (Westmead [June 2018 to May 2019]). All adult patients ($\geq$18 years of age) who presented acutely to the on-call general surgical service with clinically suspected acute diverticulitis and were admitted to the hospital were screened for eligibility during the recruitment period at each site. Admission under the general surgical service is the typical patient pathway for acute diverticulitis in both New Zealand and Australia.

Patients were given verbal information about the trial when a diagnosis of uncomplicated acute diverticulitis was clinically suspected. Potential participants were excluded if they met $\geq$2 criteria for systemic inflammatory response syndrome[15] upon presentation to hospital (temperature $<36^{\circ}$C or $>38^{\circ}$C, heart rate $>$90 beats/min, respiratory rate $>$20 breaths/min or $PaCO_3$ $<$32 mm Hg, white cell count <4 or $>12 \times 10^9$/L), were unable to give consent or answer symptom-related questions due to language barrier or cognitive impairment, had previous drug reactions to the antibiotics used in the study or had a lactose allergy, used steroids for $>$5 days prior to presentation, had been administered regular immunomodulators or biologics within the 6 months prior to presentation, used regular nonsteroidal anti-inflammatory drugs for greater than a week prior to presentation, had been administered $>$1 dose of intravenous or $>$2 doses of oral antibiotics during this illness but prior to enrollment in the study, were pregnant, had an American Society of Anesthesiologists physical status classification $\geq$4, or had CT evidence of complicated acute diverticulitis. Potential participants were also excluded if they could not be registered into the study

and start taking the study medication within 24 hours of their admission into hospital; this accounted for time taken for clinical assessment, CT confirmation of uncomplicated acute diverticulitis, and gaining informed consent.

Following CT confirmation of Hinchey 1a acute diverticulitis[16] of the descending or sigmoid colon (no evidence of perforation, abscess, or peritonitis), patients were given written and verbal information about the trial from the local study investigator, and written informed consent was obtained. A standardized protocol for the management of uncomplicated acute diverticulitis with regard to analgesia, antiemetic therapy, dietary modification, and discharge criteria was applied to all study participants. This information is available in the Supplementary Appendix.

Each study medication pack contained the initial regimen (intravenous cefuroxime 750 mg every 6 hours and oral metronidazole 400 mg 3 times a day) and oral antibiotics (Augmentin [amoxicillin/clavulanic acid] 625 mg 3 times a day), or placebo. Participants were prescribed the intravenous or oral regimen at the discretion of the surgical team, with a minimum treatment duration of 5 days of the oral regimen and a maximum treatment duration of 48 hours for the intravenous regimen and 5 days for the oral regimen (a total of 7 days of study medication). Participants requiring longer durations of treatment were regarded as having delayed recovery and started on conventional management, which included antibiotics.

The randomization process was achieved using a computer-based random number generator and was performed by the external pharmacy where the study medications were manufactured. Randomization was blocked into groups of 4 to ensure a comparable allocation to treatment and control groups. Participants, study investigators, and clinical staff were blinded to treatment allocation. The antibiotics and placebo were packaged in identical vials and bottles and labeled with a study identification number.

Demographics, past medical history, medication, and symptom history were recorded on enrollment into the study. Data were collected during the hospital admission, including vital signs and patient-reported pain score (0–10) on admission, admission blood test results, results of abdominal radiograph (if taken), administration of supportive treatment (intravenous fluids, bowel rest), any procedural intervention, length of hospital admission, 30-day readmission, intensive care unit admission, and mortality (in-hospital and 30-day).

Participants completed a symptom questionnaire every 12 hours for the first 48 hours and then daily until discharge. Participants were discharged when they were afebrile on oral study medication, able to tolerate oral diet, able to manage pain exclusively with oral analgesia, and able to mobilize safely and manage their activities of daily living. The final decision on whether participants were discharged was made by the clinical team who were blinded to allocation status. Participants were followed up with a telephone call 30 days after discharge to assess readmission, additional antibiotic prescriptions, ongoing symptoms, or adverse events. Readmission and the prescription of further courses of antibiotics were also assessed through the participants' electronic medical records.

A data monitoring committee (DMC) was set up. The DMC consisted of 2 clinicians and a biostatistician who were independent of the study and met every 6 months for the duration of the study. All serious adverse events were reported to the DMC contact person within 3 working days.

An a priori power calculation was undertaken on the basis of previously published data on the incidence and duration of hospital admissions for uncomplicated acute diverticulitis.[17] There were 204 cases of uncomplicated acute diverticulitis during this time, with a mean length of stay of 88.9 $\pm$ 70.6 hours per episode. Using these data, a power calculation was performed to determine the number of participants required to assess noninferiority of the intervention. The distribution of these data was symmetric under a logarithmic (base 10) transformation (SD = 0.3).

A change in length of stay of 24 hours was deemed to be clinically significant for both participants and for hospital services. Assuming a noninferiority margin of 24 hours, using an independent-samples t test on log-transformed length of stay data and common SD of 0.245, it was determined that 89 participants would be required in each arm to achieve 80% power and a 1-sided alpha error of .025.

Statistical analysis was performed on an intention-to-treat basis. Statistical analysis was performed using Stata for Windows version 16 (StataCorp, College Station, TX). Parametric data were expressed as mean (95% confidence interval [CI]) and nonparametric data as median (interquartile range). An independent-samples t test was used for parametric continuous variables and Mann-Whitney U test for nonparametric continuous variables. Univariate analysis was carried out using the chi-square test for categorical variables, and linear regression was performed to analyze relationships between the different variables and the primary outcome of length of stay. Results were considered statistically significant if $P < .05$.

Results

The recruitment process is summarized in Figure 1. A total of 459 participants were screened for eligibility, and 279 were excluded. In total, 180 participants were randomized to the antibiotics (n = 85) or placebo (n = 95) groups; 1 participant from each group was excluded from analysis at the request of the participants. Demographic characteristics were evenly distributed between the antibiotic and placebo groups

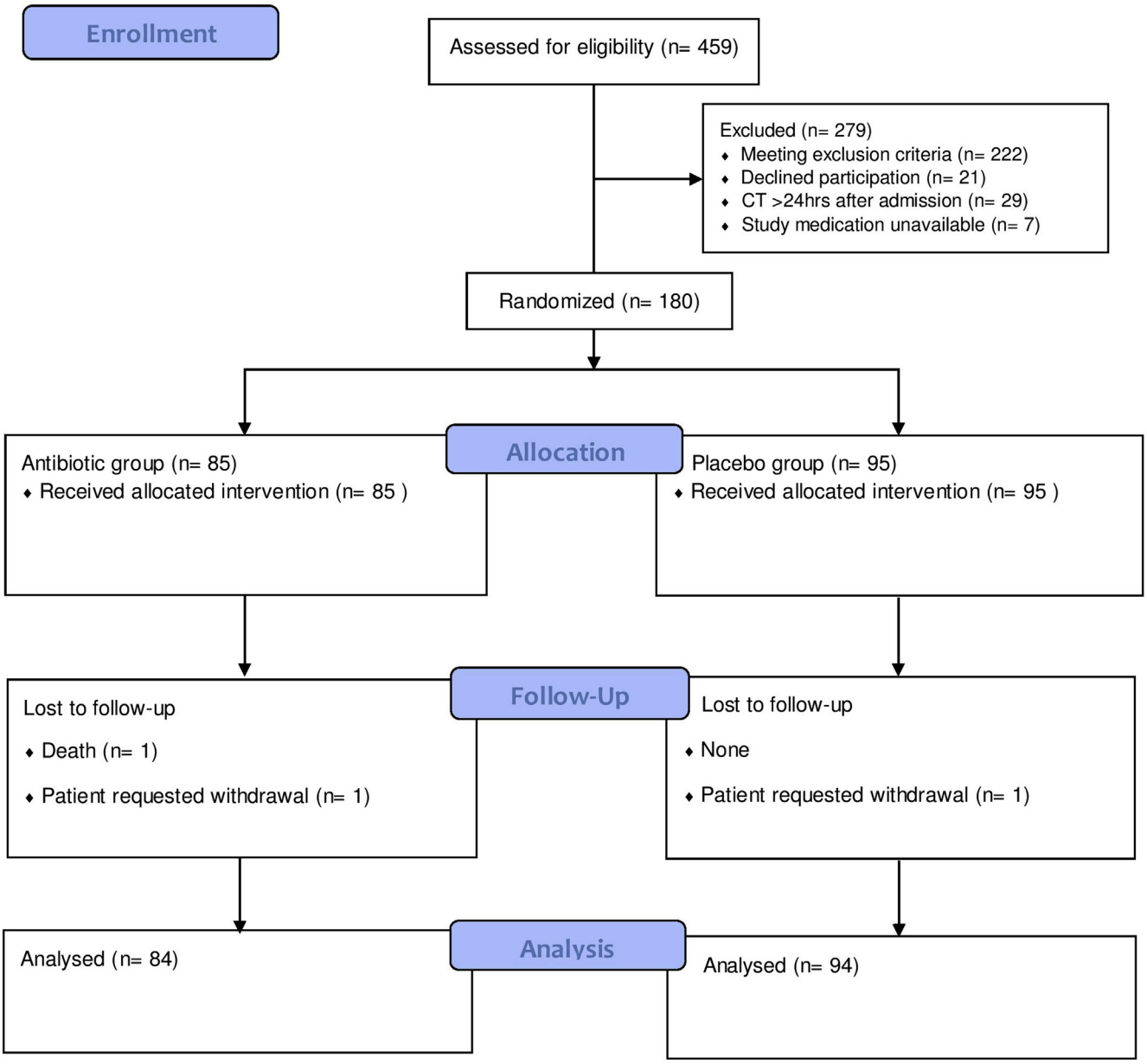

Figure 1. CONSORT 2010 flow diagram. CT, computed tomography.

(Table 1). Table 2 presents the baseline clinical characteristics of both groups at time of hospital admission. These did not differ significantly between the antibiotic and placebo groups, except that patients in the placebo group had a longer mean time to CT scan (mean 9.8 [95% CI, 6.1–8.6] hours vs 7.3 [95% CI, 8.3–11.2] hours; p = .01).

Primary Outcome

Length of hospital admission was not prolonged in the placebo group when compared with the antibiotic group (P = .15), see Table 3. The median length of hospital stay was 40.0 (95% CI, 24.4–57.6) hours in the antibiotic group and 45.8 (95% CI, 26.5–60.2) hours in the placebo group. The difference between medians (placebo group – antibiotic group) was 5.9 (95% CI, –3.7 to 15.5) hours. Similar results were found when the analysis was adjusted for the difference in time to CT scan between the groups (P = .34). The observed length of stay (42.8 hours) was shorter than that used for the sample size calculation (88.9 hours) and would imply that fewer participants would be needed to detect a difference of 24 hours, given similar SDs for the log-transformed data.

Secondary Outcomes

All but 3 participants completed 30-day follow-up, 1 participant in the antibiotic group died during the follow-up period, and 2 participants requested withdrawal from the trial (1 in each group).

Table 1. Participant Demographic Factors by Allocation Status

Characteristic	Antibiotic group (n = 84)	Placebo group (n = 94)
Age, y	56 (53–59)	59 (57–62)
Female	50 (60)	53 (56)
Ethnicity		
European	69 (82)	74 (78)
Māori	7 (8)	8 (9)
Pacific	1 (1)	2 (2)
Asian	5 (6)	4 (4)
Other	2 (2)	6 (6)

NOTE. Values are median (interquartile range) or n (%).

There were no significant differences in the secondary outcomes, as shown in Table 3. One week (6% vs 1%; $P = .07$) and 30-day readmission (6% vs 11%; $P = .3$), need for procedural intervention (2% vs 0%; $P = .1$), and mortality (1% vs 0%; $P = .3$) were not significantly different between the groups. There was no difference in mean reduction in white cell count (2.9 [95% CI, 2.3–3.5] $\times 10^9$/L vs 2.7 [95% CI, 2.2–3.3] $\times 10^9$/L; $P = .7$) or mean pain score at 24 hours (3.2 [95% CI, 2.4–3.9] vs 3.0 [95% CI, 2.3–3.7]; $P = .9$).

One participant in the antibiotic group died, after suffering a stroke and aspiration pneumonia that was unrelated to the episode of diverticulitis. Two patients (allocated to the antibiotic group) required procedural intervention. One participant had their diagnosis revised to complicated diverticulitis after worsening symptoms prompted review of their CT scan; this participant discontinued the study medication and required a Hartmann's procedure. The other participant was readmitted within 1 week with a left-sided pneumonia and associated effusion that required ultrasound-guided drainage.

Table 2. Clinical Characteristics by Allocation Status

Characteristic	Antibiotic group (n = 84)	Placebo group (n = 94)
First episode	58 (71)	64 (68)
Duration of symptoms prior to admission, d	3 (2–3)	3 (3–4)
Charlson score ≥3	15 (18)	20 (21)
Prehospital antibiotics	5 (6)	5 (5)
Time to CT scan, h[a]	7 (6–8)	10 (8–11)
Heart rate, beats/min	80 (77–83)	76.8 (74.0–79.7)
Respiratory rate, breaths/min	17 (17–18)	17 (17–17)
Temperature, °C	37 (36–37)	37 (36–37)
Pain score (0–10)	5 (4–5)	5 (4–5)
White cell count ($\times 10^9$/L)	11 (10–11)	10 (3–4)
CRP, mg/L	59 (48–69)	59 (50–69)

Values are n (%) or median (interquartile range).
CRP, C-reactive protein; CT = computated tomography.
[a]$P = .01$.

Table 3. Outcomes by Allocation Status

Outcome	Antibiotic group (n = 84)	Placebo group (n = 94)
Length of hospital stay, h	40 (24–58)	46 (26–60)
Reduction in white cell count at 24 h ($\times 10^9$/L)	3 (3–4)	3 (2–3)
Reduction in pain score (0–10) at 12 h	2 (1–3)	3 (2–3)
Reduction in pain score (0–10) at 24 h	3 (2–4)	3 (2–4)
Discontinued study treatment	8 (10)	14 (15)
Patient requested withdrawal	3 (4)	4 (4)
Nonprotocol discontinuation	1 (1)	3 (3)
Need for procedural intervention	2 (2)	0
1-wk readmission	5 (6)	1 (1)
30-d readmission	5 (6)	10 (11)
Mortality	1 (1)	0
Adverse event	10 (12)	11 (12)
Serious adverse event	3 (4)	0
Inpatient adverse events	3 (4)	8 (9)
Met SIRS criteria	1	3
Met 1 item of SIRS criteria	0	2
IV line infection	0	2
Positive MSU	0	1
Positive blood culture	1	0
Complicated AD requiring surgery	1	0
Outpatient adverse events	7 (8)	3 (3)
Readmission for AD	0	1
Pericardial effusion	1	0
UTI	1	1
Positive blood culture	1	0
Ongoing pain	1	1
Diarrhea and raised inflammatory markers	1	0
Pneumonia	1	0
Stroke	1	0

NOTE. Values are median (interquartile range), n (%), or n.
AD, acute diverticulitis; IV, intravenous; MSU, midstream urine; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection.

Twenty-two participants discontinued the study medication, 7 of these participants chose to withdraw from the study. The differences in treatment discontinuation (10% vs 15%; $P = .3$) and withdrawal rate (4% vs 4%; $P = .8$) between the study groups were not statistically significant. Reasons for discontinuation of study medication were (antibiotic vs placebo): participant's wishes (7 participants; 3 vs 4), systemic inflammatory response syndrome (4 participants; 1 vs 3), nonclinical protocol deviation (4 participants; 1 vs 3), failure to improve on study medication (1 in antibiotic group), diagnosis of complicated diverticulitis (2), positive blood culture (1), positive urine specimen (1 in placebo group), and intravenous line infection (2 in placebo group) (see Table 3).

Adverse events and serious adverse events are summarized in Table 3. There were no significant differences adverse events between the antibiotic and placebo groups (12% vs 12%; $P = .97$) and no serious adverse events (4% vs 0%; $P = .65$). There were differences in the number of inpatient and outpatient adverse events in

the placebo group compared with in the antibiotic group (9% vs 4% inpatient events, $P = .2$; 8% vs 3% outpatient events, $P = .1$). These were not statistically significant, but the study was not powered to detect differences in adverse event rate. The 3 serious adverse events include 2 participants who required procedural interventions and 1 participant who died during the study follow-up period (30 days).

Discussion

This is the first double-blinded randomized control trial of placebo vs antibiotics for the management of uncomplicated acute diverticulitis. This study demonstrates that the use of placebo is noninferior to antibiotics when comparing length of hospital admission context.

Previously, 2 open-label nonblinded randomized control trials have compared antibiotics with no antibiotics for the treatment of uncomplicated acute diverticulitis. These trials found no difference between the 2 approaches in resolution of symptoms, recurrence, complications, and length of hospital admission.[11,12] The first of these trials had a similar study population to that presented here, and they enrolled patients with CT-proven diverticulitis without "complications such as abscess, free air or fistula."[11] The other trial included participants with confined small pericolic abscesses,[12] that is, both Hinchey 1a and 1b acute diverticulitis[16,18] patients were included, while the STAND study included participants with Hinchey 1a diverticulitis only.

Length of hospital stay is an outcome that is of interest to patients, clinicians, and healthcare systems. For patients with uncomplicated acute diverticulitis, more severe outcomes such as the need for procedural management or death are rare, while extended length of hospital admission represents a more immediate concern. Clinicians must be prepared to discuss the expected clinical pathway with patients, as well as provide information about the implications of different management options. At the level of healthcare systems, length of stay represents the use of limited tertiary hospital services and the potential for iatrogenic harm during inpatient care.

This study was not powered to detect differences in other outcome measures, and there was a non–statistically significant difference in 30-day readmission to hospital (6% in the antibiotic group and 11% in the placebo group). This outcome was not reported in one of the published randomized control trials, but rates of recurrent diverticulitis during 1 year of follow-up did not differ between the antibiotics and observational treatment groups.[11] The second randomized trial found that there was no statistically significant difference in time to recovery and readmission at 6 months between the 2 groups; however, more patients in the observational group were seen in the emergency department for evaluation and outpatient care (13% vs 0.4%; $P = .006$).[12] Although these short-term differences do not appear to extend to longer-term endpoints,[19] they are nonetheless important outcomes in their own right that require closer examination.

A recent systematic review reported that selective antibiotic use did not confer any benefit over no antibiotics in uncomplicated acute diverticulitis, and not using antibiotics was associated with a shorter hospital admission.[20] Long-term follow-up of the randomized control trial of Hinchey 1a acute diverticulitis only showed no difference between the 2 approaches in terms of complications, recurrence, and surgery for diverticular disease at a median of 11 years' follow-up.[21]

Clinical guidelines have been changing to reflect this growing body of evidence. A systematic review of published clinical guidelines for diverticular disease management, published in 2018, revealed 3 differing positions on antibiotic use in uncomplicated acute diverticulitis. The guidelines recommended not using antibiotics and managing these patients as outpatients (Danish Colorectal Cancer Group, Netherlands Society of Surgeons, Italian Society of Colon and Rectal Surgery), selective antibiotic use (American Academy of Family Physicians, German Society for Gastroenterology, Digestive and Metabolic Diseases/German Society for General and Visceral Surgery, American Gastroenterological Association, Association of Polish Surgeons), or using antibiotics (American Society of Colon and Rectal Surgeons, European Association for Endoscopic Surgery).[22] The authors of the review cautioned that these guidelines referenced only 1 of the existing randomized clinical trials and suggested that further evidence, particularly further randomized clinical trials, may lead to changes in the guidelines.

Similarly, expert opinion is yet to reach consensus with regard to antibiotic use in uncomplicated acute diverticulitis. A Delphi study that recruited experts from Australasia, Asia, Europe, and North America found that internationally opinions on selective antibiotic use were divided.[23] However, the American and Australasian experts reached consensus in favor of antibiotic use.[23,24]

The decision to employ a selective approach to antibiotic use in uncomplicated acute diverticulitis must be considered in the context of the global issue of antibiotic resistance,[25] and surgeons must also take responsibility for antibiotic stewardship.[26] Antibiotic use in uncomplicated acute diverticulitis has been identified as an area in which prescribing practices could change based on new evidence.[27] Given that patients with diverticular disease continue to have high antibiotic exposure in the community,[28] this potentially represents a significant reduction in unnecessary antibiotic use.

The growing weight of evidence in favor of selective antibiotic therapy in uncomplicated acute diverticulitis necessitates that institutions revisit their position and incorporate selective antibiotic therapy into clinical protocols. These changes will need to be subjected to clinical audit to ensure that they are appropriate and optimized for

the complex clinical context. The applicability of selective antibiotic therapy in community settings also needs to be systematically investigated. Research is needed to define the patient group in which selective antibiotic use is appropriate, including refining the radiological and clinical characteristics that define uncomplicated acute diverticulitis, and identifying patients who should be exempt from this change in practice.

Limitations

This trial was powered to detect differences in length of hospital stay >24 hours, so the sample size may be inadequate to detect differences in the other clinical outcomes assessed. The follow-up after discharge from hospital was shorter than that in the 2 other randomized clinical trials (30 days compared with 24 months and 11 years),[19,21] so we may also have missed clinically significant, longer-term outcomes. The inclusion and exclusion criteria also limit the generalizability of these results to the wider population.

Conclusions

The STAND study is the first double-blind, randomized controlled trial to assess noninferiority of placebo compared with antibiotic management of uncomplicated acute diverticulitis. This result provides arguably the strongest evidence to date in support of omitting antibiotics in selected patients presenting with uncomplicated acute diverticulitis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.03.049.

References

1. Feingold D, Steele SR, Lee S, et al. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum 2014; 57:284–294.
2. Etzioni DA, Chiu VY, Cannom RR, et al. Outpatient treatment of acute diverticulitis: rates and predictors of failure. Dis Colon Rectum 2010;53:861–865.
3. Jamal Talabani A, Lydersen S, Endreseth BH, et al. Major increase in admission- and incidence rates of acute colonic diverticulitis. Int J Colorectal Dis 2014;29:937–945.
4. Li D, de Mestral C, Baxter NN, et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: a population-based analysis. Ann Surg 2014;260:423–430, discussion 430–431.
5. Vather R, Broad JB, Jaung R, et al. Demographics and trends in the acute presentation of diverticular disease: a national study. ANZ J Surg 2015;85:744–748.
6. Byrnes MC, Mazuski JE. Antimicrobial therapy for acute colonic diverticulitis. Surg Infect (Larchmt) 2009;10:143–154.
7. Brook I, Frazier EH. Aerobic and anaerobic microbiology in intra-abdominal infections associated with diverticulitis. J Med Microbiol 2000;49:827–830.
8. Alonso S, Pera M, Pares D, et al. Outpatient treatment of patients with uncomplicated acute diverticulitis. Colorectal Dis 2010;12:e278–e282.
9. Etzioni DA, Mack TM, Beart RW Jr, et al. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg 2009;249:210–217.
10. Ridgway PF, Latif A, Shabbir J, et al. Randomized controlled trial of oral vs intravenous therapy for the clinically diagnosed acute uncomplicated diverticulitis. Colorectal Dis 2009;11:941–946.
11. Chabok A, Pahlman L, Hjern F, et al. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg 2012; 99:532–539.
12. Daniels L, Unlu C, de Korte N, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg 2017; 104:52–61.
13. Estrada Ferrer O, Ruiz Edo N, Hidalgo Grau LA, et al. Selective non-antibiotic treatment in sigmoid diverticulitis: is it time to change the traditional approach? Tech Coloproctol 2016; 20:309–315.
14. Isacson D, Thorisson A, Andreasson K, et al. Outpatient, non-antibiotic management in acute uncomplicated diverticulitis: a prospective study. Int J Colorectal Dis 2015;30:1229–1234.
15. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–874.
16. Wasvary H, Turfah F, Kadro O, et al. Same hospitalization resection for acute diverticulitis. Am Surg 1999;65:632–635, discussion 636.
17. Jaung R, Kularatna M, Robertson JP, et al. Uncomplicated acute diverticulitis: identifying risk factors for severe outcomes. World J Surg 2017;41:2258–2265.
18. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg 1978;12:85–109.
19. van Dijk ST, Daniels L, Unlu C, et al. Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis. Am J Gastroenterol 2018;113:1045–1052.
20. Tandon A, Fretwell VL, Nunes QM, et al. Antibiotics vs no antibiotics in the treatment of acute uncomplicated diverticulitis – a systematic review and meta-analysis. Colorectal Dis 2018; 20:179–188.
21. Isacson D, Smedh K, Nikberg M, et al. Long-term follow-up of the AVOD randomized trial of antibiotic avoidance in uncomplicated diverticulitis. Br J Surg 2019;106:1542–1548.
22. Galetin T, Galetin A, Vestweber KH, et al. Systematic review and comparison of national and international guidelines on diverticular disease. Int J Colorectal Dis 2018;33:261–272.
23. O'Leary DP, Lynch N, Clancy C, et al. International, expert-based, consensus statement regarding the management of acute diverticulitis. JAMA Surg 2015;150:899–904.
24. Siddiqui J, Zahid A, Hong J, et al. Colorectal surgeon consensus with diverticulitis clinical practice guidelines. World J Gastrointest Surg 2017;9:224–232.
25. Goff DA, Kullar R, Goldstein EJC, et al. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. Lancet Infect Dis 2017; 17:e56–e63.

26. Sartelli M, Duane TM, Catena F, et al. Antimicrobial stewardship: a call to action for surgeons. Surg Infect 2016;17:625–631.
27. Leeds IL, Fabrizio A, Cosgrove SE, et al. Treating wisely: the surgeon's role in antibiotic stewardship. Ann Surg 2017; 265:871.
28. Broad JB, Wu Z, Ng J, et al. Diverticular disease management in primary care: How do estimates from community-dispensed antibiotics inform provision of care? PLoS One 2019;14:e0219818.

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Conflicts of Interest
The authors disclose no conflicts.

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Supplementary Appendix

Management Guidelines for Uncomplicated Diverticulitis

Antibiotics. The intravenous regimen (up to 48 hours) comprises cefuroxime 750 mg intravenously every 6 hours and oral metronidazole 400 mg 3 times a day. Oral antibiotics (on discharge or once afebrile for 24 hours) comprise Augmentin 625 mg by mouth 3 times a day for 5 days.

Analgesia. Analgesia comprises (1) paracetamol 1 g by mouth 4 times a day or as needed, (2) tramadol 50–100 mg by mouth, (3) sevredol 10–20 mg by mouth every hour, and (4) morphine 2 mg intravenously every 5 minutes for up to 10 mg.

Antiemetics. Antiemetics comprise (1) ondansetron 4–8 mg by mouth or intravenously every 8 hours and (2) metoclopramide 10 mg by mouth or intravenously every 8 hours.

Diet. Patients will be made nil by mouth with intravenous fluids while awaiting computed tomography scan. Following this (assuming uncomplicated diverticulitis), patients will be reviewed by a clinician, and in the absence of peritonism, nausea, and vomiting they will be able to eat.

Discharge. Patients will be deemed fit for discharge when (1) they are afebrile on oral antibiotics or placebo; (2) pain is controlled on oral, nonopioid analgesia; (3) they are able to tolerate an oral diet; and (4) they are able to safely mobilize and carry out activities of daily living.