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ORIGINAL RESEARCH

Antibiotics Vs Appendectomy in a Randomized Trial for Appendicitis

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ABSTRACT

Background: As an alternative to surgical removal of the appendix, antibiotic medication has been suggested for the management of appendicitis. Those participants in the study who had an appendicolith were at a greater risk for complications and appendectomy than those participants who did not have an appendicolith.

Martial and Methods: We conducted a pragmatic, nonblind, noninferiorityrandomised clinical study in patients with appendicitis at Nizams institute of medical sciences to compare antibiotic therapy (a 10-day course) with appendectomy. The European Quality of Life-5 Dimensions (EQ-5D) questionnaire was used to measure the participant's health at the 30-day mark, which was the primary outcome (scores range from 0 to 1, with higher scores indicating better health status; noninferiority margin, 0.05 points). Complications lasting 90 days and appendectomy in the antibiotics group were regarded as secondary outcomes. In subgroups created based on the presence or absence of an appendicolith, analyses were predetermined.

Results: Overall, 120adults were randomly assigned. Of these, 120 were allotted antibiotics, with 47% requiring no hospitalization for the initial medication. In the antibiotics group, by day 90, 29% of patients had undergone appendectomy (41% of those who had appendicoliths and 25% of those who did not). Complications were more common in the antibiotics group than in the appendectomy group (8.1 vs. 3.5 per 100 participants; rate ratio, 2.28; 95% CI, 1.30 to 3.98), with the difference likely attributable to the presence of appendicoliths in the antibiotics group (20.2 vs. 3.6 per 100 participants; rate ratio, 5.69; 95% CI, 2.11 to 15.38), but not in the appendectomy group (3.7 vs. When comparing the appendectomy group to the antibiotics group, the rate of serious adverse events was lower in the appendectomy group, at 3.0 per 100 people (rate ratio: 1.29; 95% confidence interval: 0.67 to 2.50).

Conclusion: Using antibiotics to treat appendicitis is equally effective as having the appendix removed surgically, according to the results of a popular way of assessing health condition. Nearly 30% of people given antibiotics had an appendectomy within 90 days. Having an appendicolith increased the likelihood of complications and the need for an appendectomy among research participants.

Keywords: Appendectomy, randomised trial, appendicitis, antibiotics, and treatment.

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INTRODUCTION

Despite the fact that successful use of antibiotic therapy as an alternative was described more than 60 years ago, appendectomy has long been the conventional treatment for appendicitis.[1] Antibiotics have been used to treat adult appendicitis in randomised trials, but their use has

been constrained by the exclusion of significant subgroups (particularly patients with appendicoliths, who may be more susceptible to complications), small sample sizes, and concerns about their generalizability.[2-6] Though many aspects of healthcare delivery, including the use of antibiotics in the treatment of appendicitis, have been suggested for reconsideration in light of the coronavirus disease pandemic of 2019 (Covid-19), according to health systems and professional societies like the American College of Surgeons.[7-10] In order to compare antibiotic medication with appendectomy in people with appendicitis, including those who had an appendicolith, we undertook the Comparison of Outcomes of Antibiotic Drugs and Appendectomy experiment. The trial's design was predicated on the understanding that different patients may place different priorities on the various outcomes of appendicitis treatment.[11-15] We present outcomes based on the first 90 days following randomization instead of when we had originally intended to report the results after all the participants had at least a year of follow-up.[16-19]

MATERIALS & METHODS

Trial Design

The protocol, which includes the statistical analysis plan, and the trial design have all been previously disclosed. In order to determine the outcomes that patients thought were most significant, patient stakeholders were involved in the design of the experiment. The authors attest to the data's correctness and completeness as well as the trial's adherence to the protocol.

Trial Population

Research coordinators at emergency rooms randomly approached adults (18 years old) with confirmed cases of appendicitis on imaging. Based on the results of a previous trial, patients with imaging evidence of an appendicolith were included in a prespecified subgroup at increased risk of complex appendicitis. All patients with localized peritonitis, recurrentappendicitis, severe phlegmon on imaging (if the surgeon determined that a more extensive operation, such as an ileocolectomy, was likely to be performed), walled-off abscess, free air or more than minimal free fluid, or evidence suggestive of neoplasm were excluded from the trial. The Supplementary Appendix, available at NEJM.org, includes additional criteria for exclusion. Imaging findings consistent with perforation were not a contraindication in the absence of these circumstances. All patients suspected of having appendicitis were screened thanks to routine site audits. The data coordinating centre randomly allocated the consenting participants to one of the treatment groups. The randomization was stratified by recruiting site and appendicolith status, and used permuted blocks (of varying sizes, 4, 6, and 8). (Present or absent). Participants who denied randomization were offered a place in a follow-up cohort study.

Treatments

Antibiotics were administered intravenously to the antibiotics group for at least 24 hours, and then orally for a total of 10 days. The antibiotics used to treat intraabdominal infections were chosen by clinical teams using recommendations from the Surgical Infection Society and the Clinical Infectious Diseases Society of India. After receiving intravenous antibiotics for 24 hours, or antibiotics with a 24-hour bioavailability, participants were either admitted to a hospital or sent home from the emergency room. Typically, patients are released from the hospital if they are able to drink fluids without trouble, have their pain under control, and show signs of clinical improvement. It was not mandatory to undergo an appendectomy unlesslocalized peritonitis, or if symptoms persisted or worsened after 48 hours of antibiotic treatment. Without them, participants were told to keep taking antibiotics and their doctors would decide whether or not to conduct an appendectomy. The approach did not address patients' worries about their appendixes or how to manage recurring appendicitis or

symptoms. Both laparoscopic and conventional (open) surgical methods were tolerated in the appendectomy group; there was no standardisation of technique. The standard protocols for preoperative, postoperative, and discharge care were followed.[20] No effort was made to standardise or monitor the dosage of analgesics or other pain drugs across the therapeutic spectrum. Participants and clinicians were given the option to switch between groups as part of the protocol.

Outcomes and Measures

The key result was the 30-day health status, which was evaluated using the European Quality of Life-5 Dimensions (EQ-5D) questionnaire18 (scores range from 0 to 1, with higher scores indicating better health status; the minimal clinically significant difference is 0.05 points19). At 24 hours after discharge, participants were to be called, and then at 1, 2, and 4 weeks, as well as quarterly for a year and then annually, they were to be polled by phone, mail, or email. Secondary outcomes included serious adverse events, National Surgical Quality Improvement Program (NSQIP)-defined complications at the time of the index treatment or during follow-up, including site-related infectious complications (defined as incisional infections or organ-space infections), particularly those that required percutaneous drainage procedures; reaction; and patient-reported resolution of symptoms, which was defined as the absence of pain, tenderness, and fever. Days spent in the hospital or emergency room due to appendicitis symptoms or treatment-associated complications, visits to the emergency room or urgent care centre for related symptoms, and days lost from work for the participant and the caregiver were also noted. An impartial safety monitor assessed serious adverse events to determine their severity and relevance to the course of treatment.

Statistical Analysis

We calculated that a sample size of 120 participants would give the trial sufficient power (>82%) to rule out a between-group difference in the EQ-5D score as small as 0.05 points, on the basis of follow-up data for 90% of the participants at 30 days, under the assumption that the mean (SD) score on the EQ-5D would be 0.900.12 after treatment for appendicitis. We evaluated 30-day EQ-5D ratings using a linear regression model with indicators for treatment group, recruiting location, and appendicolith status within an intention-to-treat framework (randomization stratification factors). Participants from the 30-day EQ-5D survey who finished all of the items were included in our main analysis. In order to examine the estimated treatment effect and 97.5% one-sided confidence interval, a noninferiority margin of 0.05 points was predetermined. The analyses of secondary outcomes did not account for multiplicity, so they should be regarded as exploratory. In the Supplementary Appendix, halting criteria are described in further detail. Three formal interim evaluations that were conducted annually during the experiment and reviewed by an independent data and safety monitoring board were not in favour of ending the research. We conducted a supplemental per-protocol analysis of EQ-5D scores and major adverse events at 30 days to address potential selection bias. (The Supplementary Appendix contains information about the interim and per-protocol analyses.) Binomial regression with a log link was used to determine relative risks for binary outcomes with adjustment for treatment group, recruitment site, and appendicolith status (if necessary), Poisson regression with robust standard errors was used to determine rate ratios for count data, and linear regression was used to determine relative risks for continuous outcomes. For each comparison, the effect sizes and related 95% confidence ranges are shown.

The incidence of appendectomy over time in the antibiotics group was plotted using a Kaplan-Meier cumulative incidence curve, both overall and according to the presence or absence of appendicoliths. As of June 4, 2020, the information is current (the final day of the 90-day survey window for the last patient). R statistical software, version 3.5.0, was used for all of the analyses.

RESULTS

Population

Beginning on May 3, 2020, and continuing until February 5, 2022, a total of 120 people were screened [Figure. 1]. Randomization was performed on a total of 120 patients, or 31% of those eligible; 76 patients were randomized to receive antibiotics, and 76 patients were assigned to have an appendectomy [Table 1].

Table 1: At a five-year follow-up, the mean hospital expenses, productivity losses, and overall expenditures for the appendectomy and antibiotic therapy groups of patients with uncomplicated acute appendicitis were all expressed in Rupies per patient.

Sr no		Appendectomy	Antibiotic Therapy	Difference	P<
One-year Follow up					
1.	Hospital Charges	200000	170000	820000	0.001
2.	Productivity Losses	220000	180000	900000	0.001
3.	Overall costs	420000	350000	1720000	0.001
Five-year follow up					
4.	Hospital charges	250000	160000	50000	0.001
5.	Productivity losses	300000	190000	80000	0.001
6.	Overall costs	550000	250000	130000	0.001

There were no appreciable variations in the individuals' sociodemographic or clinical characteristics between the two groups [Table 1]. Computed tomography (CT), either alone or in combination with magnetic resonance imaging or ultrasonography, was the imaging technique that confirmed appendicitis in 96% of the research participants. 27% of the study's participants had appendicoliths, according to imaging. For the index therapy, 51% of the individuals in the antibiotics group were admitted to the hospital, compared to 47% (ranging from 0 to 81%) of those who were sent home from the emergency room. 79% of patients who were sent home after being treated in the emergency room did so within 24 hours of being randomly assigned, whereas the remaining 2% received a different discharge outcome. The amount of time patients needed to stay in the hospital was found to be reduced more effectively by antibiotics than other treatments (e.g., were in the observational unit). 95 percent of the study participants who underwent appendectomy had to spend the night in the hospital for the index therapy, and 96 percent of the appendectomy procedures were performed using laparoscopic methods. For the index therapy, 1.33 days passed from the time of randomization until the patient receiving the antibiotics was released from the hospital or the emergency room, compared to 1.30 days for the patient receiving the appendectomy.

There were 73 patients in the antibiotic group who had 90-day follow-up data, and 11% of them had at least one additional course of antibiotics prescribed to them during that time frame. According to the sites' findings, participants in the antibiotics group adhered to the therapy at a rate of more than 99%, while those in the appendectomy group adhered at a rate of more than 90%.

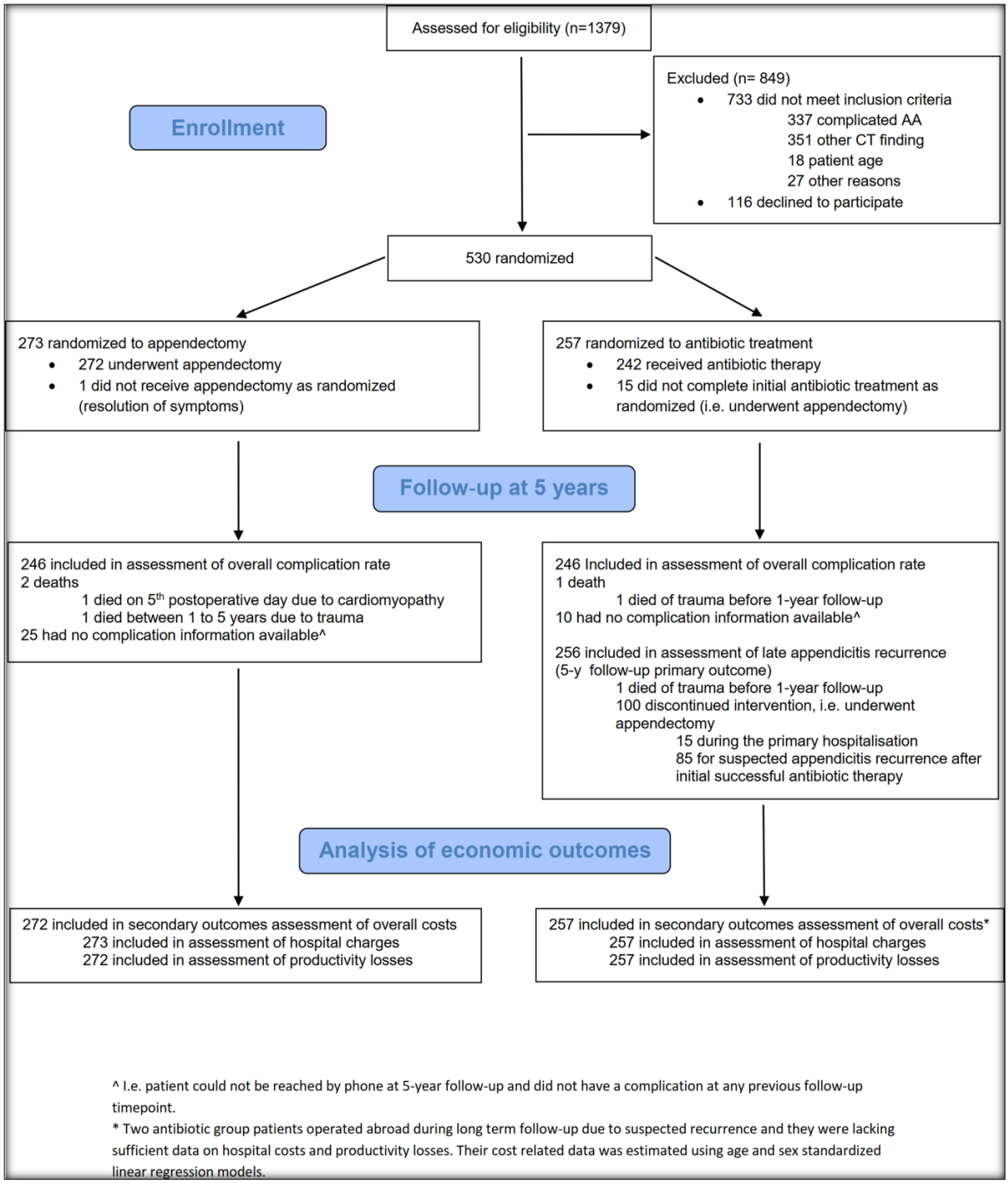

Figure 1: Path of patients in the trial

Primary and Secondary Clinical Outcomes:

The primary finding was that the antibiotics group had an EQ-5D score of 0.920.13 after 30 days, while the appendectomy group had a score of 0.910.13. These findings provide credence to the hypothesis that antibiotics are not more beneficial than appendectomy. Comparable results were found between the per-protocol analysis and the analysis in which missing primary outcome data were imputed using multiple imputation (difference, 0.01 points; 95% CI, 0.002 to 0.03).

Antibiotics were shown to be superior to placebo in the subgroup analysis comparing people with and without appendicoliths. The incidence of appendectomy was 41% in those who had

appendicoliths and 25% in those who did not have them after 90 days, with appendectomy procedures performed within 48 hours, 20% after 30 days, and 29% after 90 days in the antibiotics group. The global and appendicolith-specific results for additional secondary outcomes. Similar percentages of people in both groups stated that their symptoms had subsided (i.e., they were no longer experiencing pain, discomfort, or fever) by days 7, 14, and 30. In the antibiotics group, 9% of patients went to the emergency room or an urgent care centre following the index therapy, while in the appendectomy group, only 4% of patients did so. Two-fourths and five percent, respectively, of patients who received the index treatment needed hospitalisation. While patients in the antibiotics group missed out on an average of 1.33 days of work and those in the appendectomy group missed out on an average of 2.04 days of work, the average number of days off for caregivers was 5.26 in both groups. Two people in the antibiotics group and seven people in the appendectomy group were diagnosed with appendiceal neoplasms (mean age 47.17 years; range 21 to 74 years). Among the neoplasms were one mucocele and eight carcinomas.

DISCUSSION

Researchers from the Comparison of Outcomes of Antibiotic Drugs and Appendectomy conducted a randomised controlled trial to find out if antibiotics are more effective than surgery for treating acute, noncomplicated appendicitis. Measured mostly by the EQ-5D, a patient-reported outcome measure, this outcome was considered the most important. Several secondary outcomes were tracked and reported. Despite the fact that the experiment was designed for a longer follow-up period, the reporting for this study was discontinued after 90 days so as not to interfere with the management of appendicitis during the 2019 coronavirus illness pandemic. The 120 patients who were initially evaluated, 75 were deemed ineligible for participation. The remaining 87 patients, only 80 were randomly randomized, with 76 patients assigned to receive antibiotics and 76 patients receiving an appendectomy. In spite of widespread reports to the contrary, there was no significant difference in EQ-5D scores at 30 days between the two groups. Patients with appendicoliths who were first treated with antibiotics had poorer outcomes in the remaining objective comparisons of clinical data, which suggested substantial differences between the 2 populations. Nonoperative treatment failed for 11% of patients within 48 hours, 20% within 30 days, and 29% within 90 days. Fourteen percent of patients with appendicoliths and twenty-five percent of patients without appendicoliths in the antibiotic group required procedures by the 90-day mark. More people in the antibiotic group got sick, and it was mostly due to appendicoliths. The high incidence of appendiceal carcinoma suggests that there are tumours going undetected in the nonoperative group. Obviously, the surgical community is waiting for longer-term data, perhaps a full year's worth, as outcomes after only 90 days are considered to be fairly preliminary.[21,22]

All scientists have some degree of bias. When conducting research, scientists always strive to produce a working hypothesis and procedure that are completely free of bias. The conclusion of the Comparison of Outcomes of Antibiotic Drugs and Appendectomy collaborative's study is evident from this vantage point: "For the treatment of appendicitis, antibiotics were noninferior to appendectomy on the basis of findings of a standard health-status measure." Similar to a Rorschach test, this finding generates preconceived notions about how something should be interpreted. Antibiotics are commonly utilised in the treatment of appendicitis, as any layperson would assume. Since roughly 30% of the antibiotic group will need surgery within a specified time frame, surgeons conclude that surgical intervention is the best option. Antibiotic therapy unquestionably has benefits if we consider nonoperative management. To begin, employing antibiotics in patients who are poor surgical candidates is an enticing decision, despite the higher likelihood of antibiotic failure in patients with concomitant

illnesses. Second, if appendicitis were considered a "simple" surgical emergency less often, doctors would have more time after hours and on weekends to deal with actual emergencies.[23] Third, antibiotics can buy time, allowing 90% of individuals with appendicitis symptoms to return home and undergo surgery under better conditions if necessary (such as the wild, at sea, in space, with restricted access to medical care, etc.).

CONCLUSION

Finally, the study reassures patients and their loved ones that they can opt out of surgery with little to no impact on their lives because surgical care is always readily available. At the 90-day follow-up point, 29% of patients had undergone an appendectomy, with 25% of patients without appendicolith having their antibiotic treatment fail. While a 71% success rate may seem satisfactory at first glance, the antibiotic group actually experienced much higher rates of both acute care and hospitalisation. When you factor in the about 1% of "found" tumours in the antibiotic group that resulted in appendectomy, it seems like there is a growing argument for surgical intervention. Using the incidence rates from the appendectomy group, we estimate that there may be an additional 5 tumour patients in the nonoperative group; is this further evidence supporting the need for surgery? Twenty-five sites were involved, and more than eight thousand patients were tested in fewer than four years. The comparatively short follow-up duration in patients without appendicolith is used as evidence that both methods could be used.

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