



Antibiotics Versus Appendectomy for Acute Appendicitis: Are Antibiotics Really Noninferior?

March 2021 Annals of Emergency Medicine Journal Club

Guest Contributors

Laura Murphy, MD, MBA; Nathaniel Miller, MD; Tyler W. Barrett, MD, MSCI

0196-0644/\$-see front matter

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<https://doi.org/10.1016/j.annemergmed.2021.01.029>

Editor's Note: The Annals of Emergency Medicine Journal Club monthly provides a succinct review of high-impact articles from this and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.

ARTICLE IN REVIEW

CODA Collaborative. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med.* 2020;383:1907-1919.

What Question Does This Investigation Answer?

Is antibiotic treatment noninferior to appendectomy for acute appendicitis?

What Study Design Did the Authors Choose?

Design: Pragmatic, nonblinded, noninferiority, randomized controlled trial.

Setting: Twenty-five hospitals in the United States.

Population: A total of 1,552 adult emergency department (ED) patients with imaging-confirmed uncomplicated appendicitis absent serious systemic illness.

Primary and Secondary Outcomes: Thirty-day health status, as assessed with the use of the European Quality of Life 5–Dimensions (EQ-5D) questionnaire, along with patient-reported symptom resolution, serious adverse events, and subsequent need for appendectomy.

Sponsors: Patient-Centered Outcomes Research Institute (PCORI).

ClinicalTrials.gov Identifier: NCT02800785.

How Did the Authors Interpret the Results?

In the 1,552 patients included in the intention-to-treat analysis, use of antibiotics for treatment of appendicitis was noninferior to appendectomy according to the 30-day

EQ-5D score (0.92 [SD 0.13] versus 0.91 [SD 0.13]; difference 0.01 point; 95% confidence interval [CI] –0.001 to 0.03). In the subgroup of participants with and without appendicolith, results also showed noninferiority of antibiotics compared with appendectomy with respect to the primary outcome (0.92 versus 0.92, difference –0.01, 95% CI –0.03 to 0.02 for the appendicolith present group; 0.92 versus 0.91, difference 0.02, 95% CI 0.003 to 0.03 for appendicolith absent group). However, in the antibiotics group, 29% of participants had appendectomy performed within 90 days, including 41% with appendicolith and 25% without it. In the antibiotics group, only 51% of the patients were admitted to the hospital for index treatment; 79% of those who were discharged from the ED were discharged within 24 hours from randomization. The mean time from randomization to discharge from either the ED or hospital was similar in the 2 groups: 1.33 days for the antibiotics group and 1.30 days for the appendectomy group (rate ratio 1.00; 95% CI 0.89 to 1.13).

The rate of serious National Surgical Quality Improvement Program (NSQIP)-defined complications was higher in the antibiotics group compared with the appendectomy group (8.1 versus 3.5 per 100 participants; rate ratio 2.28; 95% CI 1.30 to 3.98); this was largely attributable to patients with appendicolith (20.2 versus 3.6 per 100 participants; rate ratio 5.69; 95% CI 2.11 to 15.38) and not to participants without an appendicolith (3.7 versus 3.5 per 100 participants; rate ratio 1.05; 95% CI 0.45 to 2.43).

The authors concluded antibiotics were noninferior to appendectomy.

How Might This Study Affect Your Clinical Practice in the ED?

Patients presenting with appendicitis can safely be treated initially with antibiotics rather than appendectomy.

However, nearly 3 of 10 patients treated with antibiotics ultimately underwent appendectomy, and increased adverse events were also observed in the antibiotic arm. Patients with appendicolith were at specifically higher risk of appendectomy and complications compared with those without appendicolith and may be more appropriate for early surgical management. The duration of follow-up of 90 days for this study limits the understanding of recurrence and long-term complications.

DISCUSSION POINTS

1. *Antibiotics were noninferior to appendectomy on the basis of the primary study outcome (30-day health status by EQ-5D questionnaire), but much of the discussion in the article centered around secondary outcomes, including complications, repeated ED visits, and hospitalizations, as well as the crossover rate of patients in the antibiotics arm who ultimately underwent appendectomy. What are some important implications of these findings?*

On the basis of the primary outcome of 30-day health status using the EQ-5D questionnaire, the use of antibiotics to treat appendicitis was noninferior to appendectomy. However, there were important differences in terms of secondary outcomes, which could have important treatment implications. Overall, approximately 30% of patients with antibiotics underwent appendectomy by 90 days, two thirds of which occurred in the first 30 days. This percentage was higher in patients with an appendicolith (41%) compared with those without one (25%). For this intention-to-treat analysis, this represents a considerable crossover rate, which may confound the noninferiority analysis.

As a matter of subjective interpretation, reporting the crossover rate as a secondary outcome implies a value judgment favoring immediate surgical intervention over delayed surgical intervention. Individuals assigned to the immediate surgery arm underwent appendectomies at enrollment and had essentially no chance of needing a subsequent appendectomy, barring some unexpected surgical complication. Therefore, one might also interpret the data focusing on the actual frequency of surgery at 30 days in the 2 groups. By definition, 100% of patients randomized to appendectomy underwent a surgical procedure, whereas 80% of those randomized to antibiotics did not.

The analysis of the secondary outcomes of short-term complications is particularly important for this study because these are potential drivers for crossover to appendectomy and are important considerations for recommending a specific treatment modality. There was

also a higher rate of NQSIP-defined complications in the antibiotic group, although this was largely driven by participants with an appendicolith present. The antibiotic treatment group also had higher rates of recurrent ED or urgent care visits than the appendectomy group, as well as higher rates of hospitalization at repeated visits (24% versus 5%). These observations were most likely driven by the eventual need for appendectomy. However, the appendectomy group also had a higher number of missed workdays, as consistent with prior studies.

Ultimately, there remains a substantial, subjective balance of risk and benefit to these strategies for management of acute appendicitis. These data are most important for further informing shared decisionmaking conversations with patients.

2. *The authors decided to publish their short-term results early with the emergence of the coronavirus disease 2019 pandemic and associated capacity constraints, as well as efforts to conserve personal protective equipment. What implications may this have for study results?*

These results support outpatient antibiotic management strategies for appendicitis. In the setting of limited hospital capacity, staffing challenges, and concern about risks of nosocomial transmission of coronavirus disease 2019 to patients and clinicians, these findings become significantly more relevant. It should be clear the former considerations are pandemic specific and reflect system dysfunction rather than a component of patient-centered care. The latter, the added risk for severe acute respiratory syndrome coronavirus 2 transmission associated with a health care setting, may be incorporated into the shared decisionmaking discussion as an added, but small, risk to the immediate-appendectomy strategy.

Ideally, if antibiotic recommendations are made, the conversations should be transparent regarding the lack of long-term outcomes, with a thorough explanation of implications and outcomes described in the 90-day follow-up. The 5-year follow-up for the Appendicitis Acuta (APPAC) trial showed a recurrence rate of 39.1% at 5 years, and this trial had much narrower inclusion criteria than the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial.^{1,2}

Section editors: Tyler W. Barrett, MD, MSCI; Ryan P. Radecki, MD, MS; Rory J. Spiegel, MD

Author affiliations: From the Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN.

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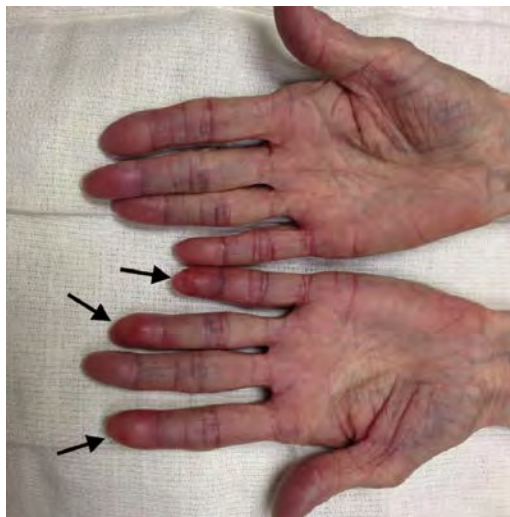
of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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