



# Nonoperative Management of Appendicitis: A Paradigm Shift?

## *Answers to the July 2017 Journal Club Questions*

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**Editor's Note:** You are reading the 58th installment of Annals of Emergency Medicine Journal Club. The article questions were published in the July issue. Information about journal club can be found at <http://www.annemergmed.com/content/journalclub>. Readers should recognize that these are suggested answers. We hope they are accurate; we know that they are not comprehensive. There are many other points that could be made about these questions or about the article in general. Questions are rated "novice" (NOV), "intermediate" (INT), and "advanced" (ADV) so that individuals planning a journal club can assign the right question to the right student. The "novice" rating does not imply that a novice should be able to spontaneously answer the question. "Novice" means we expect that someone with little background should be able to do a bit of reading, formulate an answer, and teach the material to others. Intermediate and advanced questions also will likely require some reading and research, and that reading will be sufficiently difficult that some background in clinical epidemiology will be helpful in understanding the reading and concepts. We are interested in receiving feedback about this feature. Please e-mail [journalclub@acep.org](mailto:journalclub@acep.org) with your comments.

### DISCUSSION POINTS

The concept that adult patients with acute appendicitis may be discharged from the emergency department (ED) with a prescription for antibiotics is an important potential practice change for emergency medicine and surgery.

1. A. Why would emergency physicians and surgeons (INT) be interested in investigating a nonoperative management strategy for appendicitis?
- (NOV) B. Discuss potential reasons why academic training centers may be more reluctant to adopt this nonoperative appendicitis management strategy than private hospitals.
- (INT) C. Patients with an appendicolith visualized on computed tomography (CT) imaging represent a subgroup of patients with appendicitis who may have a higher risk of failure with an antibiotics-first treatment approach. How did the authors deal with this potential for heterogeneity of treatment effect in the trial? Do you agree with this approach?

- (NOV) D. What other patient characteristics or comorbidities might discourage surgeons from recommending nonoperative management and why?
2. This was a relatively small study with a resource- and time-intensive study protocol that is unlikely to be directly generalizable to a broader population of patients with appendicitis.
  - (INT) A. Which parts of the study protocol would work in your ED? Which aspects would not? What would you suggest as alternative procedures for implementing a nonoperative management strategy for acute appendicitis?
  - (INT) B. Opine how comfortable your emergency medicine and surgery colleagues might be discharging adults with acute appendicitis from the ED.
  - (NOV) C. Among hospitals that treat underserved populations, how might problems with ensuring timely follow-up affect the disposition decision? How would you ensure necessary outpatient follow-up in this patient population?
    3. A. Contrast the definitions of efficacy and effectiveness related to a therapeutic intervention.
    - (INT) B. How did these investigators define efficacy and safety for this trial? Are those the same definitions that you would have chosen? What alternative definitions might be considered to demonstrate that nonoperative management is efficacious and safe?
    4. This study is considered a pilot trial, which is often referred to as a phase 2 trial.
      - (NOV) A. What are the purposes of pilot trials?
      - (INT) B. The follow-up phase 3 trial for this study is currently under way: the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial. Review the [clinicaltrials.gov](http://clinicaltrials.gov) entry for the CODA trial ([clinicaltrials.gov](http://clinicaltrials.gov) identifier: NCT02800785; <https://clinicaltrials.gov/ct2/show/>

NCT02800785). Discuss the differences in sample size, primary outcome, and goal of the pilot trial versus the phase 3 CODA trial. Why was the pilot trial conducted before the phase 3 trial? Why was a phase 3 trial necessary after the pilot trial?

- (NOV) C. Consider what the next steps might be in managing patients with clinical symptoms suggestive of appendicitis if the planned validation trial supports the findings of this study. How might CT use for patients with “classic appendicitis” be affected?

## ANSWER 1

*Q1. The concept that adult patients with acute appendicitis may be discharged from the emergency department (ED) with a prescription for antibiotics is an important potential practice change for emergency medicine and surgery.*

*Q1.a Why would emergency physicians and surgeons be interested in investigating a nonoperative management strategy for appendicitis?*

There are numerous examples in which emerging research has changed the surgical management of diseases. This includes the management of peptic ulcer disease, which was primarily treated with a multitude of operations to decrease gastric acid secretion until histamine receptor antagonists and proton-pump inhibitors were introduced in the 1970s and 1980s, respectively. The discovery of *Helicobacter pylori* also further clarified the pathophysiology of the disease process, and elective operations for peptic ulcer disease are now largely reserved for historical discussions because of the excellent effectiveness of medical management.<sup>2</sup> Practice guidelines for the elective surgical management of sigmoid diverticulitis also changed after years of high-quality research challenged historical practices.<sup>3</sup> An important aspect of providing optimal care is learning when not to operate.

*Q1.b Discuss potential reasons why academic training centers may be more reluctant to adopt this nonoperative appendicitis management strategy than private hospitals.*

In addition to providing patient care, academic training programs have the responsibility of training the next generation of surgeons and therefore are required to ensure that trainees have an appropriate (and regulated) number of cases to complete their surgical training. Some training programs may have concerns that managing appendicitis nonoperatively will result in trainees’ not being adequately prepared to perform an appendectomy when it is required. As an analogy, some emergency medicine training programs have expressed concern that their trainees will potentially have inadequate preparation for central venous catheter placement because of changes in sepsis care during

the past decade that have led to a large decline in central lines placed in the ED. Additionally, academic training programs may be more likely to have call schedules that better accommodate emergency or urgent operations, easing the burden of an unscheduled appendectomy compared with that of surgeons in private practice.

*Q1.c Patients with an appendicolith visualized on computed tomography (CT) imaging represent a subgroup of patients with appendicitis who may have a higher risk of failure with an antibiotics-first treatment approach. How did the authors deal with this potential for heterogeneity of treatment effect in the trial? Do you agree with this approach?*

Typically, the primary results of a clinical trial report the average effect of an intervention across the entire study population. However, the intervention may have a very different effect on individual patients; in most clinical scenarios, only a few patients can expect the average benefit reported in a clinical trial. This concept of different patients experiencing various benefit from an intervention is called heterogeneity of treatment effect.<sup>4</sup> For example, ongoing trials may demonstrate that, on average, an antibiotics-first approach for appendicitis management results in better clinical outcomes. However, patients with certain characteristics that place them at high risk for failure of the antibiotics-first approach may have better clinical outcomes if immediately treated with surgery. Whether there are characteristics that predict antibiotic failure is unknown, but several have been hypothesized, including the presence of an appendicolith and a severe systemic inflammatory response (eg, high serum C-reactive protein and proinflammatory cytokines) at appendicitis diagnosis.

In their pilot trial, Talan et al<sup>1</sup> initially excluded patients who had an appendicolith visualized on CT imaging. If all patients with an appendicolith were excluded, the trial would not have provided any information about an antibiotics-first approach for those with an appendicolith. Because available data did not clearly demonstrate increased risk for an antibiotics-first approach in patients with an appendicolith and because of the need for more data to understand the implications of an appendicolith on optimal treatment, the investigators began including patients with an appendicolith after approximately one third of the study population had been enrolled. Ultimately, 5 patients (2 in the antibiotics-first group and 3 in the appendectomy group) with an appendicolith visualized on CT were included in the trial.

Subgroup analysis is one of the basic methods of reporting heterogeneity of treatment effect. In an appendicolith subgroup analysis for the current trial, outcomes for the 2 patients with an appendicolith who were randomized to the antibiotics-first group would be

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