

# Antibiotics Only for Appendicitis?

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## ANNALS CASE

A 28-year-old otherwise healthy male patient presented with one day of right lower quadrant abdominal pain. As if he read the textbook, he reported associated nausea and anorexia. The examination was remarkable for temperature to 38.5°C (101.3°F) and right lower quadrant tenderness without peritoneal signs. Of interest to our surgery colleagues, his WBC count was 18,000 cells/mm<sup>3</sup>, and a computed tomography (CT) scan revealed an 11-mm appendix without evidence of perforation. Slam dunk! Easy case and disposition: antibiotics and call the surgeon!... until the patient said, “Hey, Doc, I don’t want surgery, and I just read on the *JAMA [Journal of the American Medical Association]* patient page that appendicitis can be treated with antibiotics alone.<sup>1</sup> Can we just do that instead?”

Can you? Should you? What’s the evidence? Is this patient a candidate? Which antibiotics? What’ll the surgeon say?

The article by Talan et al<sup>2</sup> in this month’s *Annals of Emergency Medicine* evaluated and established the feasibility of antibiotics without surgery for acute noncomplicated appendicitis, which is generally defined as absence of peritonitis and no evidence of perforation or abscess on imaging.

But wait: it is on the Internet, so it must be true, right? There must be more out there already in terms of evidence for this approach. Actually, there is a growing body of evidence addressing the safety and efficacy of antibiotic-only nonoperative treatment (AONOT) for noncomplicated appendicitis.

## THE EVIDENCE FOR NONOPERATIVE TREATMENT

Surgery has been the mainstay of appendicitis treatment for more than a century, based on the assumption that inflammation inevitably leads to perforation. However, since the discovery of antibiotics, reports of AONOT have dotted the literature. In 1956, Coldrey<sup>3</sup> reported treating 471 patients with antibiotics alone, with a recurrence rate of only 14% and one death in an elderly patient.

In the last 20 years, several studies have assessed antibiotics versus surgery in both adult and pediatric populations. But in case you don’t want to grab a giant cup of coffee and comb through decades of medical literature yourself, here’s a summary.

## WHAT’S IN THE LITERATURE?

For the adult population, there have been 7 European randomized controlled trials or quasirandomized controlled trials<sup>4-10</sup> and several subsequent meta-analyses, including 2 published this year.<sup>11-15</sup> Not all studies were included in each meta-analysis. Impressively, 1,300 total patients were included in the studies, with roughly half in the antibiotic treatment group. Upper age limits were 50 to 60 years.

For the pediatric population, there have been 4 nonrandomized controlled trials and 1 randomized controlled trial (pilot study), with ages ranging from 5 to 15 years,<sup>16-20</sup> a number of lesser-quality studies, and 2 meta-analyses.<sup>21,22</sup> More than 400 children receiving AONOT were included in the various studies.

## WHO’S A CANDIDATE?

Adult and pediatric studies included only patients with noncomplicated appendicitis. Inclusion and exclusion criteria varied across the studies, but, in general, our 28-year-old man with no health problems and CT-diagnosed noncomplicated appendicitis would meet inclusion criteria and not meet the typical exclusion criteria. The studies reviewed tended to have more stringent exclusion criteria, including but not limited to perforation or abscess, peritonitis or sepsis, steroid use, anticoagulant use, or comorbidities. In the article by Talan et al,<sup>2</sup> comorbidities

included high-risk diabetes, suspected acute coronary syndrome, heart failure, and liver and kidney disease. So, aside from being sick with acute appendicitis, you have to be pretty healthy.

### WHAT ANTIBIOTICS WERE USED?

For adults, nearly all studies included initial intravenous antibiotics, either amoxicillin plus clavulanic acid or ertapenem. Newer studies reduced the previous 2 days of inpatient intravenous antibiotics to 24 hours, and Talan et al<sup>2</sup> cinched that down to a single intravenous dose of ertapenem with 6 hours of observation. Participants in previous studies were discharged with various oral antibiotic regimens for 7 to 10 days and, in Talan et al,<sup>2</sup> with 8 days of cefdinir and metronidazole.

Pediatric studies used 1 to 3 days of intravenous antibiotics, ranging from piperacillin-tazobactam, meropenem, and cefmetazole to ciprofloxacin or metronidazole. All patients were discharged with 7 to 10 days of oral antibiotics, primarily amoxicillin.

### WHAT WERE THE OUTCOMES?

In adults, appendectomy was curative (because, as we know, patients typically only have one appendix) but was associated with a 5% to 20% complication rate during 1 year. Common complications included wound infection, abscess formation, incisional hernias, adhesions, and adverse anesthesia events.<sup>12</sup> By comparison, one meta-analysis described a 10% to 35% appendicitis recurrence rate with AONOT!<sup>12</sup> Sounds a bit like a lose-lose situation.

One meta-analysis that included a study excluded by others<sup>7</sup> found that AONOT was associated with a higher risk of peritonitis when surgery was performed. However, there was no difference in hospital stay, sick leave, or postoperative complications. Overall, the meta-analyses found no significant differences in treatment efficacy, length of stay, or risk of developing complicated appendicitis.

In pediatric patients, AONOT was initially successful in up to 97% of children. Although the length of stay was longer in the AONOT group as a result of protocol design, complications were similar in both groups. In the AONOT group, recurrent appendicitis occurred in 14%, but there were no serious adverse events. Two studies observed a significant increase in risk of AONOT failure if an appendicolith was present.

In one recent pediatric study, 37 of 102 families who participated in shared decisionmaking chose AONOT.<sup>23</sup> Its success rate at 1 year was 75.7%. No increase in complicated appendicitis was observed in AONOT patients who eventually underwent appendectomy. Overall,

children in the antibiotics group had fewer disability days (8 versus 21), as well as lower costs (\$4,219 versus \$5,029).

### DISCUSSION

Where do we go from here? Should we send our patients to the operating room or to the pharmacy? Future studies may show AONOT to be a feasible alternative to surgery in the right patient.

The potential advantages to antibiotic therapy are numerous. Antibiotic treatment is associated with lower cost and quicker recovery, with some patients returning to normal activity within 1 day.<sup>20</sup> Although hospital length of stay was longer in early studies of AONOT, shorter courses of intravenous antibiotics were effective in the more recent studies. In the study by Talan et al,<sup>2</sup> with only a single dose of an intravenous antibiotic, the total emergency department stay could be as short as 8 hours (depending on how fast the diagnosis is made)!

The elephant in the room is the risk of treatment failure or recurrence, ranging from 10% to 34%, which may be higher in nonstudy patient populations with variable treatment adherence. Increased antibiotic use could also lead to increased resistance.

A National Institutes of Health population-based study of all patients receiving a diagnosis of appendicitis by *International Classification of Diseases, Ninth Revision* code in the state of California during an 11-year period found relatively low rates of treatment failure and recurrence during a follow-up period of greater than 7 years.<sup>24</sup> Of the 3,236 patients managed nonoperatively, 5.9% experienced treatment failure (any treatment for appendicitis within 30 days of the initial diagnosis) and 4.5% experienced a recurrence (any repeated diagnosis of appendicitis greater than 30 days after initial diagnosis). There was only a 3% risk of perforation and there were no deaths. Although it's not clear why or how these patients were initially treated nonoperatively, this study does lend credence to the safety of AONOT.

A big question remains to be answered: how do we identify patients at risk for treatment failure? Who will fly and who will fail? Two pediatric studies found that the presence of an appendicolith was associated with treatment failure, but this has not been observed in other studies. And how many strikes before you're out? If appendicitis recurs, should patients be treated with antibiotics again or surgery? In one study, a second course of antibiotics was given, with most patients recovering.<sup>9</sup>

Future treatment of noncomplicated appendicitis may be similar to the treatment of nonperforated diverticulitis, with antibiotics as the mainstay of treatment. Indeed, this

was suggested by a study of the 2 disease processes by Livingston et al.<sup>25</sup>

## THE CASE

So how do we answer the question posed by our healthy patient with noncomplicated appendicitis who wants AONOT?

Our patient meets the typical inclusion and exclusion criteria for the reviewed studies and may be a candidate for AONOT. Shared decisionmaking, as described in the *JAMA* editorial, seems appropriate.<sup>23</sup> In the case of a professional athlete with an upcoming playoff game, antibiotic treatment may be preferable. On the other hand, if our patient is going abroad to a third-world country in a month, initial treatment by appendectomy may be desirable. So maybe it can be a win-win decision after all.

## BOTTOM LINE

We don't have all the evidence, but AONOT might become a reasonable approach in the appropriate patient. Be prepared to have the discussion with the patient and of course with your neighborhood friendly surgeon as well.

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