

**Maine Medical Center
Department of Emergency Medicine**

Journal Club / Research Article Summary

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ARTICLE:

- *Citation:* Salminen, P., et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis. JAMA, 2015 Jun 16; 313(23), 2340.
- *Country:* USA
- *Funding Sources:* The APPAC trial was supported by a government research grant (EVO Foundation) awarded to Turku University Hospital (in Turku, Finland).

PURPOSE:

- *Research Question(s):* Can appendicitis be successfully treated with antibiotics? Specifically, is antibiotic therapy non-inferior (< 24% effective, based on prior studies) to emergent appendectomy for treatment of acute uncomplicated appendicitis confirmed on CT scan?
- *Hypothesis:* “Appendicitis can be successfully treated with antibiotics.”

DESIGN:

- *Study Design:* Open-label (non-blinded), non-inferiority randomized clinical trial from Nov 2009 to June 2012 in Finland.
- *Independent / Research Variable:*
 - Surgical Intervention: Standard (mostly) open appendectomy
 - Antibiotic therapy: IV ertapenem (1g/d) for 3 days followed by 7 days of oral levofloxacin (500mg once daily) and metronidazole (500mg 3 times per day).
- *Dependent / Outcome Variable(s):* Successful treatment of appendicitis!
 - Primary Outcome:
 - Surgical Intervention: Successful completion of appendectomy.
 - Antibiotic Therapy: Resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up period.
 - Recurrent appendicitis was diagnosed clinically; these patients underwent appendectomy and their recurrent appendicitis was confirmed by exam of the resected specimen.
 - Secondary Outcomes:
 - Overall post-intervention complications:
 - Surgical site infection within 30 days as diagnosed by surgeon or positive wound culture, general post-op complications such as pneumonia, adverse effects of

antibiotics such as diarrhea, incisional hernia, adhesion-related problems such as bowel obstruction, persistent abdominal or incisional pain.

- Late recurrence (after 1 year) of acute appendicitis after conservative treatment
- Length of hospital stay and amount of sick leave used by the patient
- Post-intervention pain scores (VAS score range 0-10)
- Use of pain medication

SETTING / SUBJECTS:

- *Research Setting:* 6 Finnish hospitals – 3 university hospitals and 3 “central” hospitals, from November 2009 until June 2012.
- *Subjects:*
 - *Study population:* Patients aged 18 to 60 years with uncomplicated appendicitis confirmed by CT scan.
 - *Inclusion / Exclusion criteria:*
 - *Inclusion Criteria:* Patients aged 18 to 60 years with uncomplicated appendicitis confirmed by CT scan.
 - Acute appendicitis was defined as appendiceal diameter > 6mm with wall thickening and at least 1 of the following: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, fluid collections around the appendix.
 - *Exclusion Criteria:*
 - Complicated appendicitis = appendicolith (calcified deposit within the appendix), perforation, abscess, suspicion of tumor on CT.
 - Age < 18 or > 60
 - Contraindications for CT (pregnancy, lactating, allergy to contrast media/iodine, renal insufficiency, taking metformin)
 - Peritonitis; presence of serious systemic illness
 - Unable to cooperate and provide informed consent
 - *Number (control / intervention groups):*
 - 1379 patients assessed for eligibility, 849 excluded (didn't meet inclusion criteria or refused) = 530 randomized → 273 received appendectomy, 257 received antibiotic therapy.
 - *Demographics:* “The baseline characteristics of the 2 groups were similar” as seen in table 2—they don't explicitly tell us if there was any statistically significant differences in the baseline characteristics of patients in the surgical vs. antibiotic group, but they describe statistical testing of these variables in the methods.
 - On average, in both groups, 60% were male, average age was 35, pain score was 5-6; CRP, Hg, WBC, Cr were comparable; and about 60% of patients had symptoms > 18 hours.
 - *Attrition:*

- Before assessment of primary outcome:
 - *Appendectomy Group*: 1 died on fifth postoperative day due to cardiomyopathy.
 - *Antibiotic Group*: 1 died due to trauma.
- Before assessment of secondary outcomes:
 - *Appendectomy Group*: 57 lost to follow up; 1 died.
 - *Antibiotic Group*: 29 lost to follow up; 1 died.

METHODS:

- *Interventions*:
 - Surgical intervention: Standard (mostly) open appendectomy (performed using a McBurney RLQ muscle-splitting incision technique).
 - 15 patients (5.5%) underwent a laparoscopic appendectomy.
 - Prophylactic antibiotics (1.5g cefuroxime and 500mg metronidazole) were given 30 minutes before the incision was made. No further antibiotics were given unless a wound infection was suspected post-operatively.
 - Antibiotic therapy: IV ertapenem (1g/d) for 3 days followed by 7 days of oral levofloxacin (500mg once daily) and metronidazole (500mg 3 times per day).
 - “Ertapenem was chosen because of its efficacy as a monotherapy for serious intra-abdominal infections, requiring only a single, daily dose.”
 - If the surgeon suspected progressive infection, perforated appendicitis, or peritonitis on exam 12-24 hours after admission, the patient underwent appendectomy.
 - 15 of the 257 patients randomized to receive antibiotic therapy (5%) underwent appendectomy 12-24 hours after admission.
- *Study Groups*: Surgical intervention group and antibiotic therapy group, as above.
- *Instruments*: Primary and secondary outcomes measured as above.
- *Data Collection*: 13 of the authors collected data. Outcomes were assessed during hospital stay (days 0-2) and then by telephone interviews at 1 week, 2 months, and 1 year after the intervention. Patients were also instructed to contact the research hospital if they experienced any post-intervention problems. For antibiotic therapy patients who could not be reached for follow up by telephone or clinic visit, hospital records in each research hospital district were searched to determine if appendectomy was performed within 1 year.
 - The article did not describe the training of the data collectors, or provide evidence of consistency among data collectors. The article describes no changes to data collection/study protocol during the period of the study.

DATA ANALYSIS:

- *Level of Data*: X Categorical X Ordinal X Interval
- *Statistics Used*: Intention-to-treat principle was used.

- Statistical significance for categorical data was tested using the Pearson X^2 test.
- Non-inferiority for antibiotic therapy was tested using 1-sided Wald tests with an α -level of 0.05.
- Independent sample t-test was used to determine differences between groups for Hg, WBC, Cr.
- The Mann-Whitney test was used for variables not normally distributed (age, VAS pain scores, CRP level, length of hospitalization, length of sick leave).
- *What, if any, confounding variables were controlled for / adjusted for:* None

RESULTS:

Brief answers to research questions/additional findings/limitations:

Primary Outcome: 27% of patients treated with antibiotics required appendectomy within 1 year. Thus, antibiotic therapy is NOT non-inferior to open appendectomy for the treatment of acute appendicitis confirmed on CT, based on a pre-established non-inferiority margin of 24%.

- *Surgical Group:* 272 of 273 patients randomized to the appendectomy group underwent successful appendectomy = success rate of 99.6% (95% CI 98% to 100%).
- *Antibiotic Group:* 186 of 256 patients randomized to the antibiotic group did not require surgery within 1 year = success rate of 72.7% (95% CI 22.0% to 93.2%).
- “The intention to treat analysis yielded a difference in treatment efficacy between groups of -27% (95% CI, -31.6% to infinity, $P = 0.89$)” and so did not meet the author’s criteria for non-inferiority.
- Where did 24% come from?
 - Success rate of surgery was assumed to be 99%. Prior similar studies found success rates for antibiotic treatment of appendicitis ~70-80%. “Thus, we anticipated a 75% success rate in the antibiotic therapy group.”
 - Based on this, the authors established a 24% minimal clinically important difference in success between appendectomy and antibiotics. If they found the difference in success between appendectomy and antibiotic therapy to be less than 24%, they could argue that antibiotic therapy is not non-inferior to appendectomy.
 - This seems weird to me. This 24% number was chosen based on prior studies which the authors describe as having limitations in their introduction. That said, to demonstrate non-inferiority when one of your interventions has nearly a 100% success rate, you must establish some arbitrary cutoff of non-inferiority, and the authors based that cutoff on prior studies.
 - In a sense this is a moot point, because this study did not hit the seemingly arbitrary non-inferiority mark that the authors established.
- The authors argue that delayed appendectomy did NOT cause major complications, however:

- Of the 70 patients randomized to antibiotic treatment who subsequently underwent appendectomy, 5% did not have appendicitis, 83% had uncomplicated appendicitis, 10% had complicated acute appendicitis. “There were no intra-abdominal abscesses or other major complications associated with delayed appendectomy in patients randomized to antibiotic treatment.”

Secondary Outcomes: Authors looked at 4 secondary outcomes; see Table 3.

- *Overall Complications Rate:*
 - In the surgical group, 45 of 220 total patients (20.5%) had complications. In the antibiotics group, 6 of 216 total patients (2.8%) had complications. This difference was statistically significant ($P < 0.001$)
 - This is not unexpected. The complications included surgical site infections, incisional hernias, and abdominal/incisional pain or obstructive symptoms, which you only really get from surgical intervention.
 - It’s also hard to apply this to our current practice, since these were complications from open appendectomy—only 5.5% of patients underwent lap appy.
- *Length of Primary Hospital Stay:* The length of hospital stay (primary hospitalization) was statistically significantly shorter in the surgical group (25-75% CI = 2-3 days) than the antibiotic-treated group (25-75% CI = 3 days).
 - This is a no-brainer—patients in the antibiotic group were required to stay inpatient for 3 days based on study protocol.
 - This is also of limited applicability to our practice, given that many lap appys are done as bedded outpatient procedures, resulting in same-day discharge.
- *Median VAS Score:* Median VAS score was statistically significantly lower in the antibiotic group compared to the surgical group at hospital discharge and 1 week, but not at 2 months.
 - As we know from our clinical practice, the VAS score is by definition very subjective, which limits the credibility of this finding. Additionally, the VAS scores are pretty low—max of 3 at hospital discharge, and nearly all patients reported a VAS of 1 at 2 months after discharge—really, no 0s?
 - Furthermore, again lap appy, because of its non-invasive nature, is likely to result in lower VAS scores than the VAS scores seen in this study of mostly open appendectomies.
- *Median Length of Sick Leave:* Median days of sick leave for patients in the surgical group was 19, versus 7 in the antibiotic group—statistically significant.
 - This is also not surprising, but is perhaps the most credible secondary outcome supporting the antibiotic group.
 - Again, sick leave would probably be much less in patients treated with a lap appy.

IMPLICATIONS FOR PRACTICE:

- *Applicable to this clinical practice:*

- The study population in this study is generalizable to our ED population, based on demographics and inclusion criteria.
- The biggest limitation to this study in my mind, as far as applicability to our clinical practice, is the fact that the surgical intervention was open appendectomy—although this is only really affected secondary outcomes. I wonder if lap appy had been the surgical intervention, if the secondary outcomes (specifically overall complication rate, VAS score, and length of sick leave) would have been shown to be significantly superior in the antibiotic group.
- *Feasible/Clinically Relevant:*
 - If you set aside the limitations of this study, I could tell my patients that if they really don't want an appendectomy and want treatment with antibiotics instead, this would require a 3 day hospital stay for IV antibiotics (maybe CDU?) and then at the end of that they would have a 27% chance of needing an appendectomy anyway within 1 year. If I was the patient, I would choose an appendectomy every time.
 - The authors comment on this in the discussion, stating that “because appendectomy is considered the standard treatment for appendicitis, we had difficulty enrolling patients into the study.”
 - That said, 73% of patients treated with antibiotics did not require appendectomy. Although this did not meet the arbitrary non-inferiority mark set by the authors, this is a notable percentage.
 - The authors also argue that “no patient in the antibiotic group developed a serious infection resulting from delayed appendectomy, suggesting that the decision to delay appendectomy for uncomplicated acute appendicitis can be made with low likelihood of major complications resulting from delayed surgery.”

LEVEL OF EVIDENCE / DECISION FOR USE:

- Background Consider Replication Ready for use
- *Level of Evidence:*
 - Ia Evidence obtained from meta-analysis of randomized controlled trials
 - Ib Evidence obtained from at least one RCT
 - IIa Evidence obtained from at least one well-designed controlled study without randomization
 - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
 - III Well-designed non-experimental studies
 - IV Expert committee reports, opinions of experts