

Scenario:

27 y/o F w/ no significant PMH presents to the ER c/o RLQ abdominal pain x7 hours, which has been getting progressively worse. Should the treatment include appendectomy or abx only therapy if diagnosed w/ an acute uncomplicated appendicitis?

Clinical question:

In adult patients diagnosed with an uncomplicated acute appendicitis, what is the efficacy and safety of using antibiotics as a non-operative first-line treatment compared to an appendectomy?

PICO search terms:

P	I	C	O
appendicitis	antibiotics	appendectomy	symptom relief
adult population	antibiotic therapy	surgical management	recurrence
uncomplicated appendicitis	nonoperative management	surgery	complications
acute appendicitis	conservative management		efficacy
			safety
			length of recovery
			clinical outcome

Search tools and strategy used:**PubMed**

- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Best Match) - 116
- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Review & Best Match) – 29
- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Review, Best Match, publication date 5 years) - 20
- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Clinical Trial & Best Match) - 18
- Antibiotics vs Appendectomy in Appendicitis (Best Match) – 120
- Antibiotics vs Appendectomy in Appendicitis (Best Match, Review) – 4
- Antibiotics vs Appendectomy in Appendicitis (Best Match, Clinical Trial) – 27

Cochrane Library

- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Cochrane Reviews) - 1
- Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis (Trials) – 24

UpToDate

- management of acute appendicitis in adults – “Evidence for nonoperative management” – evaluated several citations from the literature for possible inclusion as well as to examine current guidelines and evidence – 23

- Since this search question is of recent medical interest, Best Match provided with better results as opposed to Most Recent. Utilizing Article types to include either Clinical Trial or Systematic Reviews allowed to narrow the list of articles. Additionally, I tried to find the most recent systematic reviews and for clinical trials to focus on the US population.

Articles Chosen:**Citation:**

1. Poprom, N., Numthavaj, P., Wilasrusmee, C., Rattanasiri, S., Attia, J., McEvoy, M., & Thakkinian, A. (2018). The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: Systematic review and network meta-analysis of randomized controlled trial. *The American Journal of Surgery*. <https://doi.org/10.1016/j.amjsurg.2018.10.009>

Type of article:

Systematic review and network meta-analysis

Abstract:

Background:

The efficacy of antibiotics in appendicitis remains controversial, and physicians are not confident in prescribing antibiotics as the first line treatment. This network meta-analysis was conducted to assess the efficacy and safety of individual antibiotics in uncomplicated appendicitis.

Methods:

Randomized controlled trials (RCTs) were identified from MEDLINE and SCOPUS databases since inception to July 2017. Studies. Network meta-analysis was applied to estimate treatment effects and safety. Probability of being the best treatment was estimated using surface under the cumulative ranking curve (SUCRA).

Results:

Among 9 RCTs meeting our inclusion criteria. A network meta-analysis indicated that those receiving antibiotics had about 12-32% lower chance of treatment success and lower risk of complication about 23-86%, especially Beta-lactamase than appendectomy. The overall appendicitis recurrence rate in the antibiotic group was about 18.2%. The SUCRA indicated that appendectomy was ranked first for treatment success and least complications, followed by Beta-lactamase.

Conclusions:

Appendectomy is still the most effective treatment in uncomplicated appendicitis, but it carries complications. Beta-lactamase might be an alternative treatment if there are any contraindications for operation.

Key points:

- Six intervention regimens were considered including Surgery (either open or laparoscopic appendectomy), Pen (penicillin), Beta-lac (beta-lactamase inhibitor), Beta-lac + Pen (beta-lactamase plus penicillin), and Cep + Met (3rd generation cephalosporin plus metronidazole/tinidazole).
- Surgery ranked best for treatment success and recurrence but ranked second worst for overall complications.
- Among antibiotics, beta-lac with/without Pen emerged as the best treatment in successful with lower complications and recurrence rates compared with other antibiotic regimens.
- The recurrence rate across all antibiotics was about 18.2%.
- If all recurrent patients had to go to appendectomy as the second line treatment, it is still a small number compared to the conventional approach that all appendicitis patients go to surgery.

Why I chose it:

I chose this article because it was recently published and being that it's a meta-analysis, it provides with a strong level of evidence. This meta-analysis has assessed both risks and benefits of treatments for uncomplicated appendicitis by comparing individual antibiotics with appendectomy. Therefore, not only were antibiotics assessed as a group as done in meta-analyses in the past, but also which individual or combination of antibiotics were best compared with appendectomy. Even though only 9 RCTs were included due to this inclusion criteria which could lead of imprecise estimation, it provides us with more clinically useful information.

Citation:

2. Poon, S. H. T., Lee, J. W. Y., NG, K. M., Chiu, G. W. Y., Wong, B. Y. K., Foo, C. C., & Law, W. L. (2017). The current management of acute uncomplicated appendicitis: should there be a change in paradigm? A systematic review of the literatures and analysis of treatment performance. *World Journal of Emergency Surgery*, 12(1). <https://doi.org/10.1186/s13017-017-0157-y>

Type of article:

Systematic review and meta-analysis

Abstract:**Introduction:**

Appendectomy has long been the mainstay of intervention for acute appendicitis, aiming at preventing perforation, peritonitis, abscess formation and recurrence. With better understanding of the disease process, non-operative management (NOM) with antibiotics alone has been proved a feasible treatment for uncomplicated appendicitis. This article aimed at systematically reviewing the available literatures and discussing the question whether NOM should replace appendectomy as the standard first-line treatment for uncomplicated appendicitis.

Method:

A search of the Embase, PubMed and Cochrane Library was performed using the keywords 'acute appendicitis' and 'antibiotic therapy'. Meta-analysis with inverse variance model for continuous variable and Mantel Haenzel Model for dichotomous variable was performed to evaluate the one-year treatment efficacy, morbidities rate, sick leave duration and length of hospital stay associated with emergency appendectomy and NOM.

Results:

Six randomized control trials were identified out of 1943 publications. NOM had a significant lower treatment efficacy rate at one year, 0.10 (95% CI 0.03–0.36, $p < 0.01$), when compared to appendectomy. The morbidities rate was comparable between the two interventions. The length of hospital stay was longer, with a mean difference of 1.08 days (95% CI 0.09–

2.07, $p = 0.03$), and the sick leave duration was shorter, a mean difference of 3.37 days (95% CI -5.90 to -0.85 days, $p < 0.01$) for NOM.

Conclusion:

The paradigm remains unchanged, that appendectomy is the gold standard of treatment for uncomplicated appendicitis, given its higher efficacy rate when compared to NOM.

Key points:

- This review demonstrated a higher efficacy for appendectomy and was consistent with earlier meta-analysis.
- Appendectomy should be the gold standard of treatment given its higher treatment success rate and shorter hospital stay.

Why I chose it:

I chose this article because it is a systematic review, published in 2017 and directly answers my search question. Specific criteria was applied for the reviewed studies, which included uncomplicated acute appendicitis, adult populations, RCTs and observational comparative studies, and all articles were published in English. This article also conducted a meta-analysis evaluating variables such as morbidity rate, sick leave duration, length of hospital stay, and treatment efficacy. The study does address that in many cases the surgery was an open appendectomy, which is difficult to generalize since many patients today receive laparoscopic appendectomy. The study suggests that high quality evidence is still needed to compare laparoscopic appendectomy and nonoperative management.

Citation:

3. Harnoss, J. C., Zelenka, I., Probst, P., Grummich, K., Müller-Lantzsch, C., Harnoss, J. M., ... Diener, M. K. (2017). Antibiotics Versus Surgical Therapy for Uncomplicated Appendicitis. *Annals of Surgery*, 265(5), 889–900. <https://doi.org/10.1097/sla.0000000000002039>

Type of article:

Systematic review and meta-analysis

Abstract:

Objective:

The aim was to investigate available evidence regarding effectiveness and safety of surgical versus conservative treatment of acute appendicitis.

Summary of Background Data: There is ongoing debate on the merits of surgical and conservative treatment for acute appendicitis.

Methods:

A systematic literature search (Cochrane Library, Medline, Embase) and hand search of retrieved reference lists up to January 2016 was conducted to identify randomized and nonrandomized studies. After critical appraisal, data were analyzed using a random-effects model in a Mantel-Haenszel test or inverse variance to calculate risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CIs).

Results:

Four trials and four cohort studies (2551 patients) were included. We found that 26.5% of patients in the conservative group needed appendectomy within 1 year, resulting in treatment effectiveness of 72.6%, significantly lower than the 99.4% in the surgical group, (RR 0.75; 95% CI 0.7–0.79; $P = 0.00001$; $I^2 = 62\%$). Overall postoperative complications were comparable (RR 0.95; 95% CI 0.35–2.58; $P = 0.91$; $I^2 = 0\%$), whereas the rate of adverse events (RR 3.18; 95% CI 1.63–6.21; $P = 0.0007$; $I^2 = 1\%$) and the incidence of complicated appendicitis (RR 2.52; 95% CI 1.17–5.43; $P = 0.02$; $I^2 = 0\%$) were significantly higher in the antibiotic treatment group. Randomized trials showed significantly longer hospital stay in the antibiotic treatment group (RR 0.3 days; 95% CI 0.07–0.53; $P = 0.009$; $I^2 = 49\%$).

Conclusions:

Although antibiotics may prevent some patients from appendectomies, surgery represents the definitive, one-time only treatment with a well-known risk profile, whereas the long-term impact of antibiotic treatment on patient quality of life and health care costs is unknown. This systematic review and meta-analysis helps physicians and patients in choosing between treatment options depending on whether they are risk averse or risk takers.

Key points:

- Fourteen full-text publications were assessed for eligibility, of which 8 were included for quantitative synthesis.
- Surgery is an effective and safe treatment of acute uncomplicated appendicitis even if patients need to be operated after an unsuccessful abx therapy.
- At the chance to avoid surgery, abx treatment increases the probability of prolonged burden of disease by longer hospital stay and readmissions.
- Available evidence does not justify routine abx treatment for acute, uncomplicated appendicitis.

Why I chose it:

I wanted to include this article in my previous PICO assignment, but I did not have access to it at the time, which I do now. This article is a systematic review and meta-analysis which offers the highest level of evidence and was published in 2017. The article mentions that based on the evidence that was collected, cephalosporins w/ imidazole compounds or gyrase inhibitors were mostly used for conservative treatment, but that the best choice for first-line abx treat for uncomplicated appendicitis remains unclear. This supports my decision to include abx tx in general as opposed to specific abx. Additionally, this article mentions that there is no follow-up data extending beyond 1 year after conservative treatment. However, I was able to find a follow-up study, which is Article #5 in this outline.

Citation:

4. Podda, M., Argenio, G., Mortola, L., Cillara, N., & Di Saverio, S. (2017). Antibiotics First Versus Surgery for Appendicitis: A US Pilot Randomized Controlled Trial Allowing Outpatient Antibiotic Management: A Little Step Toward a Patient-Centered Approach and Rethinking the Management of Acute Appendicitis. *Annals of Emergency Medicine*, 69(6), 794–795. <https://doi.org/10.1016/j.annemergmed.2017.01.037>

Type of article:

Randomized Controlled Study

Abstract:**Study objective:**

Randomized trials suggest that nonoperative treatment of uncomplicated appendicitis with antibiotics-first is safe. No trial has evaluated outpatient treatment and no US randomized trial has been conducted, to our knowledge. This pilot study assessed feasibility of a multicenter US study comparing antibiotics-first, including outpatient management, with appendectomy.

Methods:

Patients aged 5 years or older with uncomplicated appendicitis at 1 US hospital were randomized to appendectomy or intravenous ertapenem greater than or equal to 48 hours and oral cefdinir and metronidazole. Stable antibiotics-first-treated participants older than 13 years could be discharged after greater than or equal to 6-hour emergency department (ED) observation with next-day follow-up. Outcomes included 1-month major complication rate (primary) and hospital duration, pain, disability, quality of life, and hospital charges, and antibiotics-first appendectomy rate.

Results:

Of 48 eligible patients, 30 (62.5%) consented, of whom 16 (53.3%) were randomized to antibiotics-first and 14 (46.7%) to appendectomy. Median age was 33 years (range 9 to 73 years), median WBC count was 15,000/ μ L (range 6,200 to 23,100/ μ L), and median computed tomography appendiceal diameter was 10 mm (range 7 to 18 mm). Of 15 antibiotic-treated adults, 14 (93.3%) were discharged from the ED and all had symptom resolution. At 1 month, major complications occurred in 2 appendectomy participants (14.3%; 95% confidence interval [CI] 1.8% to 42.8%) and 1 antibiotics-first participant (6.3%; 95% CI 0.2% to 30.2%). Antibiotics-first participants had less total hospital time than appendectomy participants, 16.2 versus 42.1 hours, respectively. Antibiotics-first-treated participants had less pain and disability. During median 12-month follow-up, 2 of 15 antibiotics-first-treated participants (13.3%; 95% CI 3.7% to 37.9%) developed appendicitis and 1 was treated successfully with antibiotics; 1 had appendectomy. No more major complications occurred in either group.

Conclusion:

A multicenter US trial comparing antibiotics-first to appendectomy, including outpatient management, is feasible to evaluate efficacy and safety.

Key points:

- According to the National Inpatient Sample database, antibiotics-first management has been infrequently used in the US.
- Unlike in past trials, in which approximately one quarter of patients had appendectomy during 1 year of follow-up, only 1 (6.7%) participant in this pilot did.
- Trial performance measures and excellent outcomes support the feasibility of a large multicenter US randomized trial.
- The hospital stays reported were shorter than those reported from previous randomized trials, probably due to differences between European and US health care practices.
- 15 patients receiving antibiotics all recovered; 2 had recurrence; 1 was treated with appendectomy and 1 resolved with further antibiotics.

Why I chose it:

I chose this article because of its recent publication date and because according to the authors there were no RCTs conducted in the US on this subject prior to this study. Upon checking ClinicalTrials.gov, I was able to confirm this claim. Even though this study included patients aged 5 or older, it only included 1 child and the median age was 33, which matches my interest of adult population. Additionally, this RCT could lead to a large multicenter US randomized trial, potentially increasing the use of antibiotics-first management in the US.

Citation:

5. Salminen, P., Tuominen, R., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., ... Grönroos, J. M. (2018). Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. *JAMA*, 320(12), 1259. <https://doi.org/10.1001/jama.2018.13201>

Type of article:

Randomised controlled trial with long-term follow-up

Abstract:**Importance:**

Short-term results support antibiotics as an alternative to surgery for treating uncomplicated acute appendicitis, but long-term outcomes are not known.

Objective:

To determine the late recurrence rate of appendicitis after antibiotic therapy for the treatment of uncomplicated acute appendicitis.

Design, setting, and participants:

Five-year observational follow-up of patients in the Appendicitis Acuta (APPAC) multicenter randomized clinical trial comparing appendectomy with antibiotic therapy, in which 530 patients aged 18 to 60 years with computed tomography-confirmed uncomplicated acute appendicitis were randomized to undergo an appendectomy (n = 273) or receive antibiotic therapy (n = 257). The initial trial was conducted from November 2009 to June 2012 in Finland; last follow-up was September 6, 2017. This current analysis focused on assessing the 5-year outcomes for the group of patients treated with antibiotics alone.

Interventions:

Open appendectomy vs antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole.

Main outcomes and measures:

In this analysis, prespecified secondary end points reported at 5-year follow-up included late (after 1 year) appendicitis recurrence after antibiotic treatment, complications, length of hospital stay, and sick leave.

Results:

Of the 530 patients (201 women; 329 men) enrolled in the trial, 273 patients (median age, 35 years [IQR, 27-46]) were randomized to undergo appendectomy, and 257 (median age, 33 years, [IQR, 26-47]) were randomized to receive antibiotic therapy. In addition to 70 patients who initially received antibiotics but underwent appendectomy within the first year (27.3% [95% CI, 22.0%-33.2%]; 70/256), 30 additional antibiotic-treated patients (16.1% [95% CI, 11.2%-22.2%]; 30/186) underwent appendectomy between 1 and 5 years. The cumulative incidence of appendicitis recurrence was 34.0% (95% CI, 28.2%-40.1%; 87/256) at 2 years, 35.2% (95% CI, 29.3%-41.4%; 90/256) at 3 years, 37.1% (95% CI, 31.2%-43.3%; 95/256) at 4 years, and 39.1% (95% CI, 33.1%-45.3%; 100/256) at 5 years. Of the 85 patients in the antibiotic group who subsequently underwent appendectomy for recurrent appendicitis, 76 had uncomplicated appendicitis, 2 had complicated appendicitis, and 7 did not have appendicitis. At 5 years, the overall complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) was 24.4% (95% CI, 19.2%-30.3%) (n = 60/246) in the appendectomy group and 6.5% (95% CI, 3.8%-10.4%) (n = 16/246) in antibiotic group (P < .001), which calculates to 17.9 percentage points (95% CI, 11.7-24.1) higher after surgery. There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for the appendectomy group).

Conclusions and relevance:

Among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 years was 39.1%. This long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.

Key points:

- This study reports the 5-year outcomes for all the patients enrolled in the original Appendicitis Acuta (APPAC) trial (PDF attached).
- In this study of nonoperative treatment of appendicitis, 100 of the 256 patients in the antibiotic group (39.1%) ultimately underwent appendectomy after 5 years of follow-up.

- Nearly 2/3 of all patients who initially presented with uncomplicated appendicitis were successfully treated with antibiotics alone and those who ultimately developed recurrent disease did not experience any adverse outcomes related to the delay in appendectomy.
- Of the 100 patients who underwent appendectomy, 7 did not actually have appendicitis.
- Long-term follow up of patients with uncomplicated acute appendicitis suggests that initial treatment with antibiotics rather than surgery may be a feasible alternative.

Why I chose it:

This is a long-term follow-up of the RCT trial published in 2015 (PDF of which is included). As a reference, in the original study “most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications.” I chose not to include the original RCT study because it was conducted in Finland, and the RCT that I did include was conducted in the US, allowing for more generalizability. However, this follow-up study was published in 2018 and looked at a five-year long-term follow-up, which according to the authors of Article #3 was missing and was essential to the question.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/studies, cohort definition etc.)	Outcomes(s) studied	Key Findings	Limitations and Biases
<p>1. Poprom, N., Numthavaj, P., Wilasrusmee, C., Rattanasiri, S., Attia, J., McEvoy, M., & Thakkinstian, A. (2018)</p>	<p>Systematic review and network meta-analysis of RCT</p>	<ul style="list-style-type: none"> - MEDLINE and SCOPUS databases were used to identify RCTs since inception of the study to July 2017 - RCTs published in English were selected if they met all the following criteria: <ul style="list-style-type: none"> - Studies in children or adult patients who were diagnosed as uncomplicated appendicitis - Compared effects of any pair of intervention including antibiotics (e.g., 3rd Cephalosporin, Beta-lactamase, Penicillin, and Metronidazole/Tinidazole), open appendectomy, and laparoscopic appendectomy - Reported at least 1 of following outcomes of interest including initial successful of treatment, overall complications, recurrence, and length of stay - Two reviewers independently selected studies by screening titles and abstracts - Any disagreement was resolved by a third author - 9 RCTs met the inclusion criteria 	<ul style="list-style-type: none"> - To assess the efficacy and safety of individual antibiotics in uncomplicated appendicitis - Abx were assessed as a group and also by which individual/combination abx were best compared w/ appendectomy - The primary outcomes of interest were initial treatment success, recurrence and overall complications - The secondary outcomes were recurrence and length of stay 	<ul style="list-style-type: none"> - Six intervention regimens were considered including: <ol style="list-style-type: none"> 1) surgery (either open or laparoscopic appendectomy) 2) penicillin (Pen) 3) beta-lactamase inhibitor (Beta-lac) 4) beta-lactamase plus penicillin (Beta-lac & Pen) 5) beta-lactamase plus metronidazole/tinidazole (Beta-lac & Met) 6) 3rd generation cephalosporin plus metronidazole/tinidazole (Cep & Met) - Surgery ranked best for treatment success and recurrence but ranked second worst for overall complications - Among antibiotics, beta-lac with/without Pen emerged as the best treatment in successful with lower complications and recurrence rates compared with other antibiotic regimens - Penicillin was inferior to surgery and other antibiotics with respect to all outcomes - Appendectomy was ranked first followed by Beta-lac with/without Pen for treatment success - Beta-lac and Cep & Met were ranked first and second in lowest complications 	<ul style="list-style-type: none"> - Even though various abx were used, they were collapsed into one category when compared with appendectomy - Cochrane risk of bias tool was used to asses for bias and if there was any disagreement, a third party was included - The risk of recurrence was compared among the abx group only - only 9 RCTs were included because of the strict limitations, which could lead to imprecise estimation of relative treatment effects - no uniform use of abx, different studies used different combinations of abx, which could cause hospital acquired C. Diff and change in the intestinal flora, especially w/ cephalosporin use - trials of the included RCTs only followed pts for a maximum of one year - definition of outcomes is defined differently across studies - studied pts were different across studies - authors did not report any potential conflicts of interest - link to supplementary data is provided

					- 5 RTCs were conducted in Sweden, 1 in Finland, 1 in France, 1 in Missouri, and 1 in the US from 2017, but it included children and adults
2. Poon, S. H. T., Lee, J. W. Y., NG, K. M., Chiu, G. W. Y., Wong, B. Y. K., Foo, C. C., & Law, W. L. (2017)	Systematic review and meta-analysis	<ul style="list-style-type: none"> - Embase, PubMed and Cochrane Library search was performed using the keywords “acute appendicitis” and “antibiotic therapy” - 6 RCTs were identified out of 1943 - Inclusion criteria included: <ol style="list-style-type: none"> 1) uncomplicated acute appendicitis (excluded perforation and intra-abdominal abscess) 2) mainly focus on adult population 3) full article published in English 4) RCTs & prospective comparative studies 	<ul style="list-style-type: none"> - Aimed at systematically reviewing the available literatures and discussing the question whether non-operative management should replace appendectomy as the standard first-line treatment for uncomplicated appendicitis - primary outcomes that were measured included the success rate, morbidities rate, length of hospital stay, and loss of work associated with the two treatment modalities - treatment success was defined as resolution of appendicitis without the development of complications or recurrence necessitating interventions 	<ul style="list-style-type: none"> - Non-operative management had a significant lower treatment efficacy rate at one year when compared to appendectomy - The morbidities rate was comparable between the two interventions - Non-operative management had a longer hospital stay and a shorter sick leave duration was shorter - The paradigm remains unchanged, that appendectomy is the gold standard of treatment for uncomplicated appendicitis, given its higher efficacy rate when compared to non-operative management - appendectomy offers definitive histology and provides a chance to diagnose rare appendiceal and extra-appendiceal pathologies 	<ul style="list-style-type: none"> - There was diagnostic inaccuracy as some of the recruited patients were suffering from complicated appendicitis - The authors do address the bias of the included studied in their clinical appraisal, including CT not applied for dx of appendicitis, excluded female pts, high cross over rate from non-operative management to appendectomy - One article was retracted due to plagiarism and was not included in the concluding 6 RCTs - choice of operative approach (open or laparoscopic) was not standardized and was often up to surgeons’ discretion - no results of the long-term efficacy are available - there was no reported conflict of interest
3. Harnoss, J. C., Zelienska, I., Probst, P., Grummich, K., Müller-Lantzsch, C., Harnoss, J. M., ... Diener, M. K. (2017)	Systematic review and meta-analysis	<ul style="list-style-type: none"> - Cochrane library, Medline and Embase were used for the systematic literature search - hand search was conducted to retrieve article up to January 2016 where randomized and nonrandomized studies were chosen 	<ul style="list-style-type: none"> - The aim was to investigate available evidence regarding effectiveness and safety of surgical versus conservative treatment of acute appendicitis - The outcomes measures that were assessed include: 	<ul style="list-style-type: none"> - 26.5% of patients in the conservative group needed appendectomy within 1 year, resulting in treatment effectiveness of 72.6%, significantly lower than the 99.4% in the surgical group - Overall postoperative complications were similar 	<ul style="list-style-type: none"> - the search strategy strictly adhered to the protocol, details of which are freely accessible as well - risk of bias was assessed using the Cochrane risk of bias tool - One trial was evaluated as a nonrandomized cohort study as opposed to RCT due to

		<ul style="list-style-type: none"> - Four trials and four cohort studies (2551 patients) were included - For inclusion, all studies had to contain a clear definition of the diagnosis “uncomplicated appendicitis” - All studies related to complicated appendicitis or treatments in children were excluded - Only studies that reported at least the primary outcome or one of the secondary outcomes were included 	<ol style="list-style-type: none"> 1) effectiveness (treatment effectiveness, complication-free treatment success) 2) Safety (postoperative complications, adverse events of abx treatment, complicated progress of disease) 3) length of hospital stay and costs 	<ul style="list-style-type: none"> - rate of adverse events and the incidence of complicated appendicitis were significantly higher in the abx treatment group - randomized trials showed significantly longer hospital stay in the abx treatment group - surgery represents the definitive, one-time only treatment with a well-known risk profile - the low rate of false-negative appendectomies clearly shows that unnecessary surgery is rare in these times of improved diagnostic tools 	<p>the cross-over, where pts and surgeons were allowed to change the tx plan</p> <ul style="list-style-type: none"> - failure of initial tx was counted as a complication of postinterventional course
<p>4. Podda, M., Argenio, G., Mortola, L., Cillara, N., & Di Saverio, S. (2017)</p>	RCT	<ul style="list-style-type: none"> - patients aged 5 years or older with uncomplicated appendicitis at 1 US hospital were randomized to appendectomy or IV ertapenem greater than or equal to 48 hours and oral cefdinir and metronidazole - of 48 eligible patients, 30 consented, of whom 16 were randomized to antibiotics-first and 14 to appendectomy - median age was 33 years - patients were enrolled from March to September 2015 at Olive View–UCLA Medical Center, a County of Los Angeles UCLA-affiliated hospital - the Olive View–UCLA institutional review board approved the study and protocol amendments 	<ul style="list-style-type: none"> - this pilot study assessed feasibility of a multicenter US study comparing antibiotics-first, including outpatient management, with appendectomy - primary outcome included 1-month major complication rate - Major complications were defined as: <ol style="list-style-type: none"> 1) organ/space infection, including peritonitis 2) wound dehiscence 3) pneumonia 4) unplanned intubation 5) pulmonary embolism 6) mechanical ventilation for more than 48 hours 7) progressive renal insufficiency 8) major urinary tract infection 	<ul style="list-style-type: none"> - Antibiotics-first participants had less total hospital time than appendectomy participants - Antibiotics-first-treated participants had less pain and disability - During median 12-month follow-up, 2 of 15 antibiotics-first-treated participants developed appendicitis and 1 was treated successfully with antibiotics, 1 had appendectomy - All but 1 of the 15 adult patients randomized to antibiotics-first were successfully managed as outpatients after a minimum 6-hour ED observation period after triage - at 1 month, major complications occurred in 2 	<ul style="list-style-type: none"> - investigators were unblinded because a fake surgery would be unethical, which could had led to bias of management of participants and outcome assessments - very small sample size was used, which mostly included Hispanic pts, which might not make findings generalizable - since all abx first tx pts were d/c from the ED, there are fewer opportunities for surgeons to observe pts to assess the initial abx failure

		<p>- ED patients were included who had the presumptive diagnosis of acute appendicitis by the ED attending physician and who met the following criteria:</p> <ol style="list-style-type: none"> 1) age 5 years or older 2) radiographic diagnosis of uncomplicated appendicitis by computed tomography (CT) and/or ultrasonography as read by an attending radiologist and performed within 24 hours of consent 3) clinical diagnosis of uncomplicated appendicitis by a surgical teaching service supervised by an attending surgeon 4) ability to provide written informed consent in English or Spanish (for participants ages 5 to 17 years, consent from parent/guardian and assent, when appropriate) 	<ol style="list-style-type: none"> 9) malignant hyperthermia 10) stroke/cerebral vascular accident 11) coma for more than 24 hours 12) cardiac arrest 13) myocardial infarction 14) bleeding requiring transfusion 15) severe sepsis and septic shock 16) deep venous thrombosis 17) unexpected re-operation related to appendicitis 18) dehydration requiring hospitalization 19) unplanned hospitalization related to a complication of appendicitis or its treatment after initial hospitalization 20) antibiotic-related adverse event, including colitis, requiring hospitalization <p>- secondary outcomes included hospital duration, pain, disability, quality of life, and hospital charges, and antibiotics-first appendectomy rate</p>	<p>appendectomy participants and 1 antibiotics-first participant</p> <p>- Antibiotic-treated participants experienced more, mostly mild, adverse events, including diarrhea, headache, and nausea</p>	
<p>5. Salminen, P., Tuominen, R., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., ... Grönroos, J. M. (2018)</p>	<p>Randomised controlled trial with long-term follow-up</p>	<p>- 5-year observational f/u</p> <p>- 540 pts aged 18-60 years old w/ CT confirmed uncomplicated acute appendicitis were randomized to undergo an appendectomy (273) or abx therapy (257)</p> <p>- trial was conducted from November 2009 – June 2012 in Finland</p> <p>- abx therapy included IV ertapenem for 3 days followed</p>	<p>- This study looked at the late recurrence rate of appendicitis after abx therapy for the tx of uncomplicated acute appendicitis</p> <p>- 5 year outcomes was assessed for the pts treated w/ abx alone</p>	<p>- In addition to 70 patients who initially received antibiotics but underwent appendectomy within the first year, 30 additional antibiotic-treated patients underwent appendectomy between 1 and 5 years</p> <p>- The cumulative incidence of appendicitis recurrence was:</p> <ul style="list-style-type: none"> - 34.0% at 2 years - 35.2% at 3 years 	<p>- the study was conducted in Finland, which might not be generalizable to the US population</p> <p>- open appendectomies were performed vs opposed to laparoscopic appendectomies which have a very low complication rate and are associated w/ rapid return to normal function</p> <p>- however, at the time the study was conducted, open</p>

		<p>by 7 days of oral levofloxacin and metronidazole</p>		<ul style="list-style-type: none"> - 37.1% at 4 years - 39.1% at 5 years - Of the 85 patients in the antibiotic group who subsequently underwent appendectomy for recurrent appendicitis: - 76 had uncomplicated appendicitis - 2 had complicated appendicitis - 7 did not have appendicitis - At 5 years, the overall complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) was 24.4% in the appendectomy group and 6.5% in antibiotic group - There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for the appendectomy group) - No patient initially treated with antibiotics, who ultimately developed recurrent appendicitis, had any complications related to the delay in surgery 	<p>operation was the standard approach in the Finnish healthcare system</p> <ul style="list-style-type: none"> - large number of pts were included from several different medical centers - a nearly complete f/u of 5 years, but still some people were missing - there was no protocol guiding decision making regarding performance of an appendectomy following randomization - median hospital stay was 3 days for the abx group, which could have been excessive
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Conclusions(s):

1. Poprom, N., Numthavaj, P., Wilasrusmee, C., Rattanasiri, S., Attia, J., McEvoy, M., & Thakkinstian, A. (2018)	<ul style="list-style-type: none">- Appendectomy is still the most effective treatment in uncomplicated appendicitis but it carries complications.- Beta-lactamase, might be an alternative treatment if there are any contraindications for operation.
2. Poon, S. H. T., Lee, J. W. Y., NG, K. M., Chiu, G. W. Y., Wong, B. Y. K., Foo, C. C., & Law, W. L. (2017)	<ul style="list-style-type: none">- Appendectomy is the gold standard of treatment for uncomplicated appendicitis, given its higher efficacy rate when compared to non-operative management.- Appendectomy offers definitive histology and provides a chance to diagnose rare appendiceal and extra-appendiceal pathologies.
3. Harnoss, J. C., Zelenka, I., Probst, P., Grummich, K., Müller-Lantsch, C., Harnoss, J. M., ... Diener, M. K. (2017)	<ul style="list-style-type: none">- Although antibiotics may prevent some patients from appendectomies, surgery represents the definitive, one-time only treatment with a well-known risk profile.- The low rate of false-negative appendectomies clearly shows that unnecessary surgery is rare in these times of improved diagnostic tools.
4. Podda, M., Argenio, G., Mortola, L., Cillara, N., & Di Saverio, S. (2017)	<ul style="list-style-type: none">- All but 1 of the 15 adult patients randomized to antibiotics-first were successfully managed as outpatients after a minimum 6-hour ED observation period after triage.- at 1-month, major complications occurred in 2 appendectomy participants and 1 antibiotics-first participant.- This trial performance measures and excellent outcomes support the feasibility of a future large multicenter US randomized trial.
5. Salminen, P., Tuominen, R., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., ... Grönroos, J. M. (2018)	<ul style="list-style-type: none">- Among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 years was 39.1%.- This long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.
The overall conclusion is that while there is significant evidence of the benefit of using abx as a non-operative first-line treatment, appendectomy is still more superior at this time.	

Clinical Bottom Line:

In adult patients diagnosed with an uncomplicated acute appendicitis, what is the efficacy and safety of using antibiotics as a non-operative first-line treatment compared to an appendectomy?

Overall, I think the articles that I have included provide strong level of evidence, 3 of them being systematic reviews and meta-analyses, 1 being RCT performed in the US, and 1 being a 5-year follow-up of abx first-line tx. While they did include several limitations discussed above, it is difficult for the studies in the systematic reviews to be similar among all criteria, and since I was only able to find 1 RCT performed in the US as of yet, I was not surprised about the small sample size.

The clinical bottom line is that at this time, appendectomy is more superior compared to antibiotic first-line treatment. Appendectomy has long been the mainstay of intervention for acute appendicitis, aiming at preventing perforation, peritonitis, abscess formation and recurrence. Additionally, appendectomy can provide with the histologic demonstration of carcinoma, which could be missed w/ abx first-line therapy. Abx first-line therapy could also lead to C. Diff diarrhea especially from cephalosporin use.

Instead of replacing antibiotic therapy with the current approach of appendectomy, it could still be an available treatment option, especially if there is a contraindication for surgery. Additionally, antibiotic treatment can also be an option for those patients with a strong preference for avoiding appendectomy. Since there is a lack of studies that examine this search question, patients that are interested in antibiotics-first approach should be encouraged to participate in clinical trials, especially in the US so that more data can be gathered. Managing appendicitis with antibiotics without hospitalization could also significantly reduce costs, and spare patients from postoperative pain, surgical risks and wound complications. Therefore, patients should be informed of all available treatment options in order to make an informed decision on an individual basis depending on clinician's and patient's judgement and discussion.

Essentially, a large US-based multicenter RCT that includes a diverse population in which imaging is routinely used, appendectomies are performed laparoscopically, early discharge is promoted, patients are offered antibiotic retreatment and a long-term follow-up of at least 2 years would greatly contribute to the already existing evidence.