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Review

The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: Systematic review and network meta-analysis of randomized controlled trial

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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.

Introduction

Appendicitis is the most common urgent condition in general surgical practice with an incidence ~100/100,000/year, and higher prevalence in men than women (8.6% versus 6.7%).[1,2] Standard treatment is appendectomy (i.e., open and laparoscopic appendectomy). About 310,000 appendectomies are performed/year in the United States, of which 250,000 have definite appendicitis,[3] giving a negative appendectomy rate of about 15%–30%.[4]

Appendectomy itself is associated with intra and post-operative morbidities including vascular injuries, urinary tract complications, hematomas, colonic fistulas, surgical site infections, adhesions, bowel obstructions, and significant length of hospital stay.[4–6] The post-operative complication rate ranges from 2% to 23% and more than 3% of patients are readmitted with intestinal obstruction and post-operative adhesion.[7–9]

Conservative treatment with antibiotics is an alternative choice for appendicitis; although the risk of failure is about 13% higher, but the risk of complications is lower. For instance, the odds of overall complications, bowel obstruction, and reoperation were 0.24 (95% CI: 0.13 to 0.44), 0.35 (95%CI: 0.17 to 0.71), and 0.17 (95%CI: 0.04 to 0.75) respectively, when compared to appendectomy.[10] In addition, management might be more cost-effective with antibiotics than appendectomy.[11]

Conservative treatment with antibiotics for uncomplicated appendicitis is a topical issue in general surgery and there are 3,[12–14] 13,[15–27] and 1[10] systematic reviews in children, adults and mixed populations (children and adults) respectively. Among 13

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systematic reviews in adults, 10 reviews considered only randomized controlled trials (RCT) published during 1995–2015 with the number of included RCTs ranging from 3 to 6. Among them, all except one review[16] pooled efficacy and complications between antibiotics and appendectomy applying meta-analysis. Although various antibiotics (i.e. 3rd generation of cephalosporin, metronidazole, penicillin, and beta-lactamase) had been used, they were collapsed into one category when compared with appendectomy. We therefore conducted a systematic review and network meta-analysis to assess both the efficacy and safety between individual antibiotics and appendectomy. Probabilities of being the best treatment option, i.e., high efficacy and safety, were estimated and ranked.

Material and methods

The systematic review and network meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines extension for network meta-analysis,[28] and was registered at PROSPERO (NO. CRD42017072585).

Literature and search strategy

Studies were identified from MEDLINE and SCOPUS databases since inception to July 2017. The search terms were constructed based on components of Patient, Intervention, Comparator, and Outcome (PICO) as described in supplementary table s1a and s1b.

Study selection

RCTs published in English were selected if they met all the following criteria:

- 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 (LOS).

Two reviewers (NP and CW) independently selected studies by screening titles and abstracts. If a decision could be not made, the full texts were retrieved and reviewed. Any disagreement was resolved by consensus, with adjudication by a third author (AT).

Interventions

Any antibiotic administered intravenously as the first-line treatment for 24–48 h was considered. Antibiotics were categorized by class as follows: 3rd generation cephalosporin plus metronidazole/tinidazole (Cep + Met), beta-lactamase plus metronidazole/tinidazole (Beta-lac + Met), beta-lactamase plus penicillin (Beta-lac + Pen), beta-lactamase inhibitor (Beta-lac), and penicillin (Pen). The standard comparator was surgery (Surg), which could be either open or laparoscopic appendectomy. Details of antibiotic dosage are described in supplementary table s2.

Outcome of interests

The primary outcomes of interest were initial treatment success, recurrence and overall complications, which were defined according to the original studies. Briefly, the initial treatment success was defined as therapeutic efficacy at initial hospitalization, which was pathologically confirmed appendicitis after surgery for appendectomy but this was variously defined in antibiotic uses including improvement with subsequent hospital discharge in that admission, dischargeable without recurrence or need for surgery within 1–3 months or even 1 year of follow up. Overall complications included any of the following: clinical wound infection occurring within 30 days after the appendectomy which was diagnosed by a surgeon with/without a positive bacteria culture,[2,29–31] wound rupture/dehiscence,[30–32] wound hernia,[2,7] peritonitis,[31] abscess,[7,32] re-operation,[31,32] small bowel obstruction,[2,7,32] venous thromboembolism (VTE),[31] postoperative cardiac problems,[31,32] and ileocecal resection[31] (Supplementary Table s3). Recurrence was considered and compared only among antibiotic uses, which was defined as recurrence of appendicitis within 1 month to 1 year.

The secondary outcomes were recurrence and LOS. The recurrence was defined as diagnosis of appendectomy again after initial treatment; LOS was defined as number of days of primary admission.

Data extraction

The data extraction was performed by two independent authors. The characteristics of studies and patients were extracted and included study design, follow up period, type of subjects, type of antibiotics, type of surgical treatment, type of outcome reported, number of subjects, mean age, sex, body mass index (BMI, kg/m^2), duration of symptoms, body temperature, C-reactive protein (CRP, mg/L), WBC, ($\times$109/L), and neutrophils ($\times$109/L).

Risk of bias assessments

The Cochrane risk of bias tool[33] assessed 6 domains including selection bias, performance bias, attrition bias, detection bias, reporting bias; in case of disagreement, consensus including a third party was sought.

Statistical analysis

Direct meta-analysis

For each study, risk ratio (RR) and mean difference (MD) along with their variances were estimated for dichotomous outcomes (i.e., efficacy/treatment successful, overall complications, and recurrence) and continuous outcomes (i.e., pain, and LOS), respectively. These RRs and MDs were then pooled across studies.

Heterogeneity was checked using the Cochrane's Q test and I^2 statistic. If heterogeneity was present (p-value of Q test < 0.1 and $I^2 < 25\%$), a random-effects model was used; otherwise a fixed-effects model was used. Sources of heterogeneity were explored by fitting each covariate (i.e., gender, age, duration of symptom, body temperature, BMI, CRP, WBC count, and neutrophil) in a meta-regression model if data were available. If adding that variable decreased the I^2, that variable was considered a source of heterogeneity, and sub-group analysis was performed accordingly.

Publication bias was assessed using a funnel plot and Egger test. If the funnel was asymmetrical, a contour enhanced funnel plot was constructed to distinguish whether heterogeneity or publication bias was the cause of asymmetry.

Network meta-analysis (NMA)

A two-stage NMA was applied to assess relative treatment

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effects (e.g., ln(RR) or MD) as follows[34,35]: First, a binary or linear regression was used to estimate relative treatment effects and the variance-covariance for each individual study using open appendectomy as the reference. Second, a multivariate random-effect meta-analysis with consistency model was used to pool relative treatment effects (e.g., ln(RR), MD) across the studies. Mixed relative treatment comparisons were then estimated.

Transitivity (also called similarity or exchangeability) was checked by exploring distributions of co-variables or effect modifiers (e.g., gender, age, BMI) between each pair of interventions and studies. Consistency, agreement between direct and indirect comparisons, was assessed using a design-treatment interaction inconsistency model. A global Chi-square test was used to test inconsistency. If inconsistency was present, the characteristics of studies were explored. The probability of being the best treatment was estimated and ranked using surface under the cumulative ranking curve (SUCRA). Publication bias was assessed using an adjusted funnel plot. All analyses were performed using STATA 14.2. P value less than 0.05 was the threshold for statistical significance, except for heterogeneity where $P < 0.1$ was used.

Results

A total of 3498 studies were identified from PUBMED and SCOPUS databases, and 2545 articles remained after deleting duplicates, consisting of 17 systematic reviews with/without meta-analyses (SR/MA) and 2528 individual studies. Among 17 SRs/MAs, there were 52 included studies but only 9 RCTs[2,7,29–32,36–38] met our inclusion criteria, see Fig. 1. Among 2528 individual studies, the same 9 RCTs[2,7,29–32,36–38] were identified.

Characteristics information of eligible studies

The characteristics of the 9 RCTs[2,7,29–32,36–38] are described in Table 1. Among 9 RCTs, 2[30,36] and 6[2,7,29,31,32,37,38] RCTs studied children and adults respectively, while the remaining RCT(37) included a mixed population (although the majority of patients were adults). This RCT was therefore combined with adult studies in further analyses. Among the 2 Pediatric RCTs,[30,36] the interventions were Cep + Met (N = 1),[36] and Beta-lac + Met (N = 1),[30] which were compared with laparoscopic appendectomy for treatment success,[30,36] LOS,[30,36] recurrence,[30] and complications.[30] The mean age of children ranged from 9.5 to 11 years and WBC count ranged from 14.00×10^9/L to 17.20×10^9/L.

Among the 7 adult RCTs,[2,7,29,31,32,37,38] interventions and comparators were as follows: Cep + Met versus appendectomy (N = 3),[29,32,37] Beta-lac versus appendectomy (N = 2),[2,31] Beta-lac + Pen versus appendectomy (N = 1),[38] and Pen versus appendectomy (N = 1).[7]

All 7 RCTs[2,7,29,31,32,37,38] in adults reported treatment success and LOS, whereas overall complications and recurrence were reported in 6 RCTs[2,7,29,31,32,37] and 4 RCTs[2,7,29,37] respectively. The follow-up period of all included studies were 12 months with a percent lost follow-up of between 1% and 10%, see Table 1. Mean age ranged from 18.5 to 38 years. Most RCTs reported mean CRP and WBC count, which ranged from 35 to 80.5 mg/L and 11.9 to 14.4×10^9/L, respectively. Further quantitative analyses were focused on adult RCTs only.

Risk of bias assessment

Risk of bias assessments were performed, see supplementary table s4. Among the 7 adult RCTs, all studies were considered at low risk of bias for blinding of outcome assessment (detection bias), and selective reporting (reporting bias). About 70% of RCTs were at low risk of bias for random sequence generation, allocation concealment (selection bias), and incomplete outcome data (attrition bias). All RCTs were at high risk of bias for blinding of participants but this was because those who received operations could be not blinded.

Direct meta-analysis (DMA)

DMA was performed by pooling effects of Cep + Met vs Surg on treatment success (n = 3), complication (n = 3), and LOS (n = 3)., see supplementary table s6a-6c. The pooled RRs for treatment success and overall complications were 0.70 (0.49, 1.01) and 0.39 (95%CI: 0.22, 0.70), respectively. LOSs were not much different between Cep + Met vs Surg with a pooled MD of 0.17 (−0.23, 0.56), see supplementary table s6c.

Network meta-analysis

Treatment success

Network meta-analysis was performed using data from 7 RCTs[2,7,29,31,32,37,38] with 2017 patients, see Fig. 2a and supplementary Table s6a. Relative treatment comparisons were pooled indicating all antibiotic regimens had lower treatment success compared with appendectomy, with pooled RRs between 0.68 and 0.88, although none of them was statistically significant, see Table 2. Among antibiotics, Beta-lac + Pen and Beta-lac inhibitor seemed to be better than Cep + Met with pooled RRs of 1.24 (0.73, 2.10) and 1.16 (0.75, 1.78), respectively although these were not significant. In addition, both regimens were also better than Pen alone with corresponding pooled RRs of 1.30 (0.68, 2.47) and 1.21 (0.69, 2.13) respectively. However, none of these were statistically significant. The probability of being the best treatment was Surg, followed by Beta-lac + Pen and Beta-lac inhibitor with SUCRAs of 89.9, 61.9, and 50, respectively (see Table 2). The adjusted funnel plot showed little asymmetry (see Fig. 3a).

A sensitivity analysis was perform considering percentage of complicated appendicitis finding after operation, which ranged from 2.7% to 35% and 1.5%–60% in antibiotics and appendectomy, respectively. Excluding one study with highest complicated appendicitis in antibiotic group (i.e., 35%) from the overall analysis did not change much results. Beta-lac + Pen and Beta-lac inhibitor were still better than Cep + Met with the pooled RRs of 1.21 (0.63, 2.31) and 1.13 (0.66, 1.94), respectively, although these were not significant. Likewise, the two regimens were also better than Pen with corresponding pooled RRs of 1.30 (0.61, 2.75) and 1.21 (0.63, 2.34).

Overall complications

Seven RCTs[2,7,29,31,32,37,38] with 2017 patients compared overall complications between antibiotics and appendectomy (see Fig. 2b), which consisted of Cep + Met versus Surg (N = 3, n = 661),[29,32,37] Beta-lac + Pen versus Surg (N = 1, n = 553),[38] Beta-lac versus Surg (N = 2, n = 560),[2,31] and Pen versus Surg (N = 1, n = 243).[7] Data for these comparisons are described in Supplementary table s6b. Compared to appendectomy, Beta-lac and Cep + Met had significantly lower risk of complications (RR 0.14 (0.05, 0.37) and 0.35 (0.16, 0.75) respectively) whereas Pen had about 3 fold (RR 2.98 (0.29, 30.36) higher risk but this was not statistically significant (see Table 3). Comparing among antibiotics, Pen had significantly higher risk of developing complications than Beta-lac and Cep + Met, with a pooled RRs of 21.06 (1.70, 260.77) and 8.52 (0.74, 98.01), although the latter was not statistically significant. In

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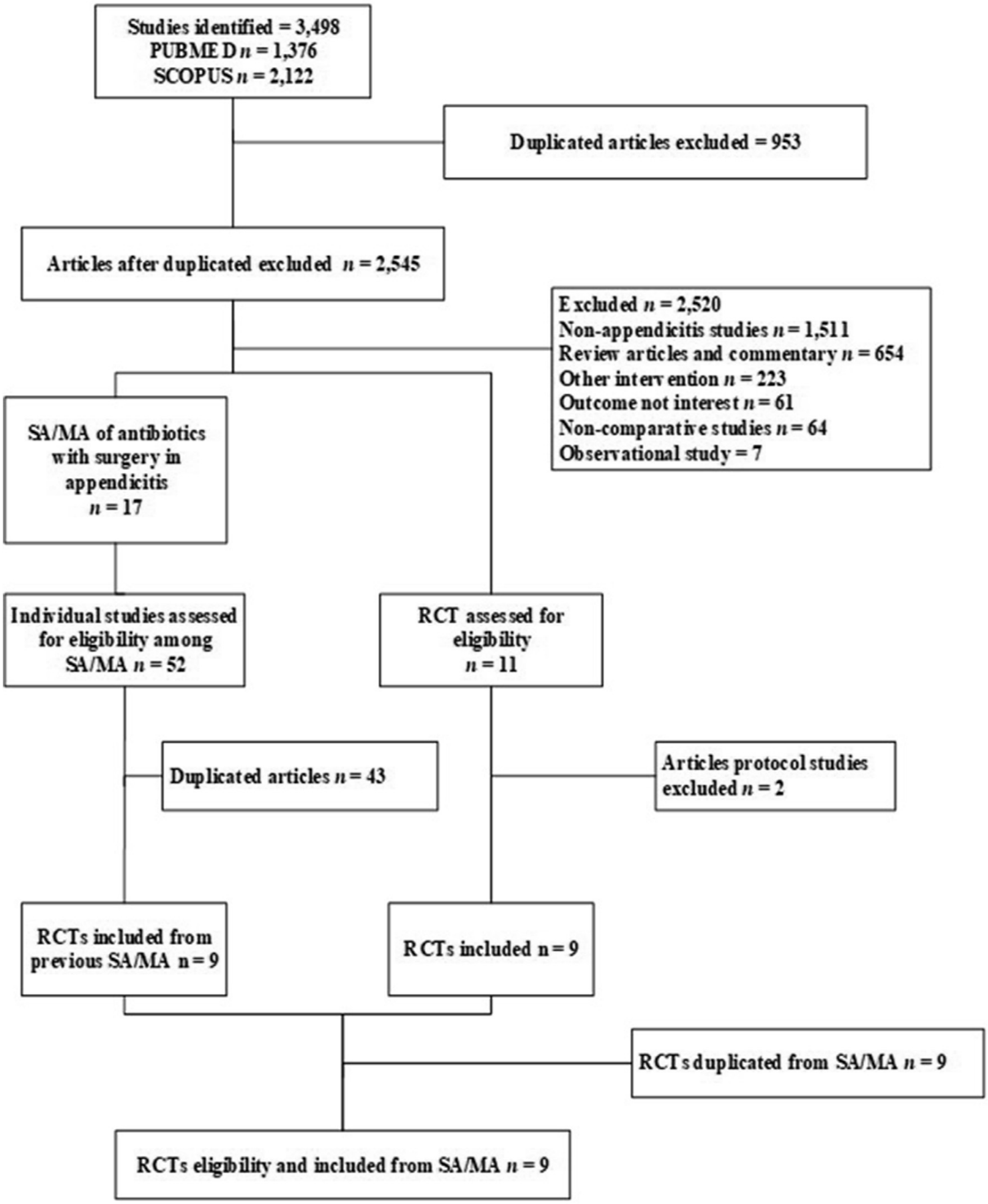

Fig. 1. Flow diagram of selection of studies.

addition, adding Pen to Beta-lac significantly increased the risk of complication when compared to beta-lac alone, with a pooled RR of 5.43 (1.44, 20.42) (see Table 3).

The lowest risk of complications was in the Beta-lac group followed by Cep + Met, with SUCRAs of 97.5 and 72.6, respectively (see Table 3). The adjusted funnel showed no evidence of inconsistency (see Fig. 3b).

Recurrence

Data from 5 RCTs 3[2,31,38] with 1725 patients were used to compare relative treatment effects including Cep + Met vs Surg (N = 1, n = 369),[32] Beta-lact + Pen vs Surg (N = 1, n = 553),[38] Beta-lac vs Surg (N = 2, n = 560),[2,31] Pen vs Surg (N = 1, n = 243),[7] (see Supplementary table s6c). The pooled incidence of recurrence across antibiotic groups was 18.3% (95% CI: 8.5%, 27.9%). All treatments were mapped (see Supplementary figure s1a) and mixed treatment comparisons indicated a highly significant risk of recurrence for all antibiotics compared to appendectomy, with pooled RRs ranging from about 12 to 87, see Supplementary table s7a. Compared to other antibiotics, Pen had higher risk of recurrence, with pooled RRs of about 3–7, although these were not

Table 1
Characteristics of included RCTs.

Author, year	Type of patients	Comparator	Intervention		Country	Outcomes	Follow-up (months)	No. of subjects	Mean age (years)	Mean BMI (kg/m^2)	Mean CRP (mg/L)	Mean WBC ($\times 10^9$/L)	Mean neutrophil ($\times 10^9$/L)	Mean time recurrence (months)	Second line treatment	Appendix diameter (mm)	% complicated AP[a]	Improvement AP	% lost F/U
			IV Antibiotic	Oral Antibiotic															
Eriksson S, 1995[29]	Adults	Open/ laparoscopic appendectomy	Cefotaxim + tinidazol	Ofloxacin 200 mg + tinidazole 500 mg	Sweden	Successful Complications Recurrence LOS	12	40	36.00	NR	40.50	13.90	NR	7	Surgery	>6	60 in surgery	US + Lab	NR
Styrud J, 2006[37]	Adults	Open/ laparoscopic appendectomy	Cefotaxim + tinidazol.	Ofloxacin 200 mg + tinidazole 500 mg	Sweden	Successful Complication Recurrence LOS	12	252	18-50	NR	54.50	12.50	NR	4	Surgery	0	5	Lab	NR
HanssonJ, 2009[32]	Adults	Open/ laparoscopic appendectomy	Cefotaxim + metronidazole	Ciprofloxacin 500 mg + metronidazole 400 mg	Sweden	successful Complication LOS	12	369	38.00	NR	54.50	13.10	NR	5	Surgery	0	20	CT	10
St.Peter SD, 2010[36]	Children	Laparoscopic appendectomy	Ceftriaxone + metronidazole	NR	Missouri	successful LOS	12	40	9.45	18.80	NR	17.20	NR	NR	NR	0	100[b]	CT	NR
Vons C, 2011[7]	Adults	Open/ laparoscopic appendectomy	Amoxicillin + Clavulanic acid	Amoxicillin + Clavulanic acid 3 g	France	Successful Complication Recurrence LOS	12	239	32.50	23.50	NR	NR	13.40	5	Surgery	6-15	12.6	CT	10
HanssonJ, 2012[38]	Adults	Open/ laparoscopic appendectomy	Piperacillin + tazobactam	Ciprofloxacin 500 mg + metronidazole 400 mg	Sweden	successful LOS	12	558	34.20	NR	56.80	12.80	10.40	NR	NR	0	24.5	CT	1
Saliminen P, 2015[2]	Adults	Open/ laparoscopic appendectomy	Ertapenem	Levofloxacin 500 mg + metronidazole 500 mg	Finland	Successful Complication Recurrence LOS	12	530	36.60	NR	34.90	11.90	NR	3	Surgery	>6	2.1	CT	1
Svensson JF, 2015[30]	Children	Laparoscopic appendectomy	Meropenem + Metronidazole	Ciprofloxacin 20 mg + metronidazole 20 mg	Sweden	Successful Complication Recurrence LOS	12	50	11.04	NR	59.60	14.00	11.50	9	Surgery	9-10	24	CT	NR
Talan DA, 2017[31]	Mixed children and adults	Open/ laparoscopic appendectomy	Ertapenem	Cefdinir 300 mg + metronidazole 500 mg	United State	Successful Complication LOS	12	30	37.90	NR	80.50	14.40	78.70	13	Surgery	7-18	17.2	CT	NR

[a] AP; appendicitis, CT; computer tomography, US; ultrasonography, Lab; laboratory results, NR; Not reported.
[b] Included only complicated appendicitis.

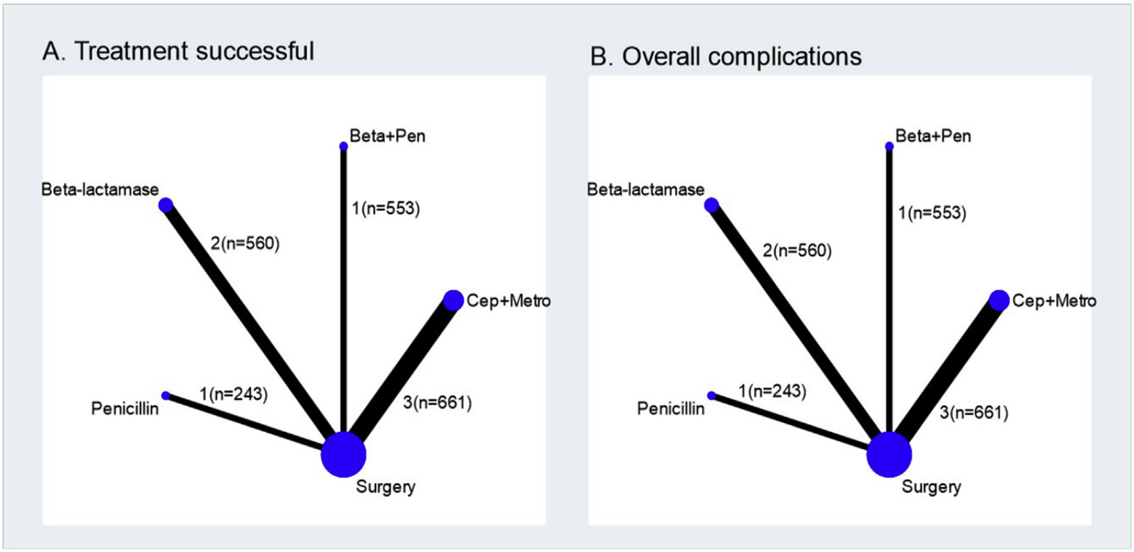

Fig. 2. Network of eligible treatment comparison mapping by outcomes a) Treatment successful. b) Overall complications.

statistically significant. Surgery had the lowest risk of recurrence, followed by Cep + Met regimen. An adjusted funnel plot showed no evidence of bias or inconsistency (see Supplementary figure s2a).

LOS

All 7 RCTs with 2017 patients compared mean differences of LOS between intervention groups, see Supplementary table s6d. A network map was constructed (see Supplementary figure s1b) and mixed treatment comparisons were estimated (see Supplementary table s7b) indicating Beta-lac + Pen had about 0.6 (−1.05,-0.15) days significantly shorter LOS than Surg whereas the rest had about 0.16−0.92 days longer but none was statistically significant. Among antibiotics, Beta-lac + Pen had about −0.76 (−1.41,-0.11) and −1.52 (−2.62,-0.42) significantly shorter LOS than Cep + Met and Pen, respectively. Beta-lac + Pen (SUCRA 98.9), was ranked as shortest LOS followed by Surg (SUCRA = 55.5), see Supplementary table s7b. Additionally, the adjusted funnel plot showed no evidence of inconsistency or study size effect (see Supplementary figure s2b).

Discussion

We conducted a systematic review and network meta-analysis to compare important clinical outcomes (i.e., treatment success, overall complications, and recurrence) between antibiotics and surgical treatment of uncomplicated appendicitis in adults. Six intervention regimens were considered including Surg (either open or laparoscopic appendectomy), Pen, Beta-lac, Beta-lac + Pen, and Cep + Met. Surg 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.

Although Beta-lac had about 18% lower treatment success than Surg, it had much lower risk for complication occurrences whereas LOS was not different. These findings were consistent with previous studies in which antibiotic treatments had fewer complications,[15,16,21–26] but stand in contrast to other studies which found shorter LOS.[12,23,25,26] However, post-operation complications were very rare which could occur early or late after operation. For instance, infections occurred within 30 days with a range of 2%−13%[2,7,32,38] whereas late and major complications were obstruction/adhesion, intra-abdominal abscess, and re-operation with the rates of 4%,[2] 4%,[32] and 2%,[38] respectively. In addition, wound rupture, wound hernia, and lesion of bladder after operation were reported about 0%−5%.[2,32,38] Although these complications were common in surgery than antibiotic treatments, they were mostly treatable.

Our finding of low recurrence in the surgical group was similar to previous findings,[12,21,24,27] undoubtedly because the appendix

Table 2
Mixed treatment comparisons for treatment successful.

Interventions	Surg	Cep+Met	Beta-lac+Pen	Beta-lac	Pen
Surg	]89.9; 60.4[	0.71)0.53,0.94(	0.88)0.56,1.38(	0.82)0.59,1.14(	0.68)0.43,1.07(
Cep+Met	1.41)1.07,1.87(	]25.9; 0.6[	1.24)0.73,2.10(	1.16)0.75,1.78(	0.95)0.56,1.64(
Beta-lac+Pen	1.14)0.73,1.79(	0.81)0.48,1.37(	]61.9; 27.6[	0.93)0.53,1.63(	0.77)0.40,1.47(
Beta-lac	1.22)0.88,1.70(	0.86)0.56,1.33(	1.07)0.61,1.87(	]50; 8.3[	0.83)0.47,1.45(
Pen	1.48)0.93,2.35(	1.05)0.61,1.80(	1.30)0.68,2.47(	1.21)0.69,2.13(	]23.5; 3.1[

Value above off the diagonal cells are risk ratio with 95% confidence intervals (in round parentheses) of treatment successful of antibiotics in the column heading compared with the reference in the left row. The values > 1.00 show benefit of treatment successful compared with reference treatment. Values in diagonal line in the square brackets are surface under the cumulative ranking curve area; percentage probability of being best treatment.

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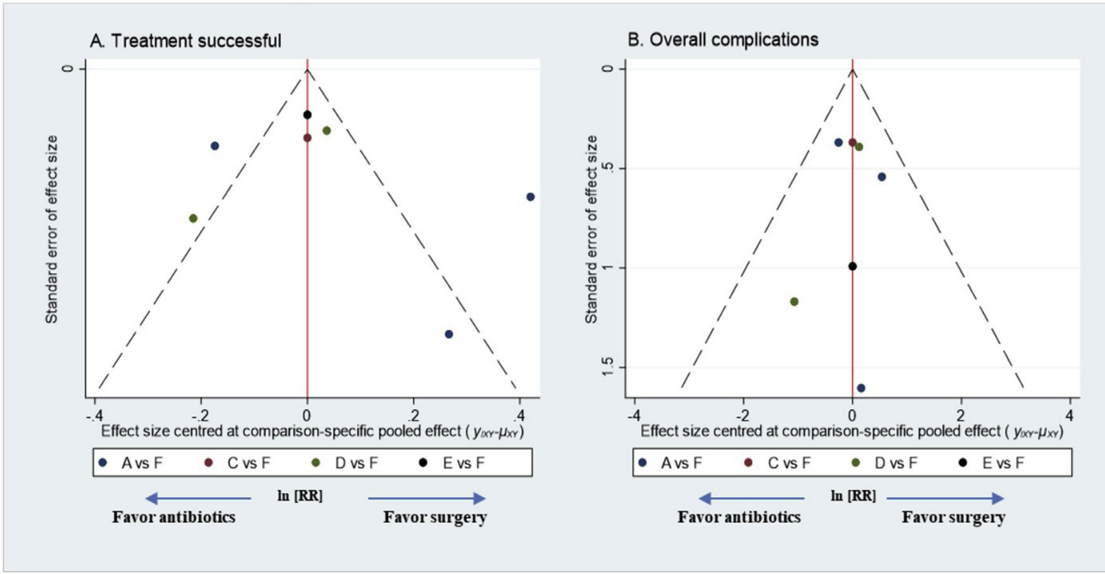

Fig. 3. Adjusted funnel plot a) Treatment successful. b) Overall complications.

was removed after surgery. Therefore, the risk of recurrence should be compared among antibiotic groups only; this indicated that Cep + Met had about 36%, 54%, and 86% lower risk of recurrence than Beta-lac + Pen, Beta-lac, and Pen respectively. In addition, consideration of antibiotic choices should take into account both risk and benefit. For instance, Beta-lac was better than Cep + Met in treatment efficacy and lower complications, although it had about 50% higher chance of disease recurrence. As a result, Beta-lactamase with/without penicillin might be recommended as a first-line antibiotic treatment of uncomplicated appendicitis where surgery is not possible.

The recurrence rate across all antibiotics was about 18.2%, which is higher than a recent RCT (~13.3%)[31] but lower than the previous meta-analysis (~27.4%).[17] If all of these recurrent patients have to go to appendectomy as the second line treatment, this is still a small number compared to the conventional approach that all appendicitis patients go to surgery. In addition, 4[2,7,32,37] out of 9 studies reported that disability and time away from work were shorter in antibiotic treatments than appendectomy with a range of 5–9 days and 6–19 days, respectively. However, we could not apply NMA because of insufficient data. To answer whether antibiotics will be more benefit than risk when compare to appendectomy should be further evaluated by well conducted RCT alongside with cost-effectiveness/utility analysis, that should consider longer time horizon (say at least 1 year) and also allow to adjust for factors may affect on disease recurrence in an antibiotics such as type of appendicitis (complicated versus uncomplicated appendicitis), use of drainage, underlying disease (e.g., obesity, diabetes), etc.

Although a standard of care for both of uncomplicated and complicated appendicitis was surgical management as for a clinical practice guideline,[39] a conservative treatment by antibiotics might be another choice of care for uncomplicated acute appendicitis depending on clinician's and patient's judgment and discussion[39] with the results from imaging before treatment including ultrasonography or computer tomography to confirm uncomplicated acute appendicitis. However, ultrasound and/or compute tomography might face with false negative results, in which complicated appendicitis finding after appendectomy was varied from 2.7% to 35% in the antibiotic group. Although a sensitivity analysis by excluding the study with highest complicated appendicitis did not change the outcome of successful, this is still needs to proof if antibiotics work as good as appendectomy by considering only uncomplicated appendicitis. Doing this is required individual patient data to adjust for this factor.

Another issue that should be considered is the development of hospital-acquired *Clostridium difficile* colitis and the change in intestinal flora among antibiotic users.[40] Among broad-spectrum antibiotics, cephalosporins have a higher risk of development of *C. difficile* infection compared to penicillin combinations.[41] As trials in this review followed patients for a maximum of one year, long term changes in antibiotics resistance, particularly among different types of antibiotics, remain unknown and rates of *C. difficile* diarrhea were not systematically collected.

Our study had some strengths. To our knowledge, this is the first meta-analysis that has assessed both risks and benefits of treatments for uncomplicated appendicitis by comparing individual antibiotics with appendectomy; the NMA covers the broad range of treatment options that are relevant clinically. We also aimed to assess not only antibiotics as a group but also which individual/combination antibiotics were best compared with appendectomy. To achieve this aim, we had to keep individual antibiotics without lumping them all to one group as previous meta-analyses did.[10,12–27] Although this gives more clinically useful information, it also means that only a few RCTs were included for each comparison, resulting in an imprecise estimation of relative treatment effects. This review should be updated as new RCTs are published. However, few limitations could be not avoided. First, definition of outcomes (i.e., successful, complication, recurrence) had been defined differently across studies in which they could not be re-defined based on summary/aggregated data and thus might affect on clinical efficacy and generalizability. Second, studied patients were different across studies, i.e., 1 study[36] included only complicated appendicitis, 2 studies[29,32] mentioned to include acute appendicitis which might mix complicated and uncomplicated appendicitis, whereas the rest 6 studies[2,7,30,31,37,38] included only uncomplicated appendicitis. Among 8 later studies, complicated appendicitis was found in operations which ranged from 2.7% to 35% and 1.5%–60% in antibiotic and surgery groups, respectively. Contamination of complicated appendicitis might result in lowering successful and increasing recurrence rates among

Table 3
Mixed treatment comparisons for overall complications.

Interventions	Surg	Cep+Met	Beta-lac+Pen	Beta-lac	Pen
Surg	]27.7; 0.0[	0.35)0.16,0.75(	0.77)0.31,1.90(	0.14)0.05,0.37(	2.98)0.29,30.36(
Cep+Met	2.86)1.34,6.11(	]72.6; 7.4[	2.19)0.67,7.14(	0.40)0.11,1.48(	8.52)0.74,98.01(
Beta-lac+Pen	1.30)0.53,3.23(	0.46)0.14,1.48(	]41.9; 0.5[	0.18)0.05,0.69(	3.88)0.32,46.96(
Beta-lac	7.08)2.69,18.63(	2.47)0.68,9.03(	5.43)1.44,20.42(	]97.5; 90.8[	21.06)1.70,260.77(
Pen	0.34)0.03,3.43(	0.12)0.01,1.35(	0.26)0.02,3.12(	0.05)0.00,0.59(	]10.2; 1.3[

Value above off the diagonal cells are risk ratio with 95% confidence intervals (in round parentheses) of overall complications of antibiotics in the column heading compared with the reference in the left row. The values < 1.00 show benefit of less complications compared with reference treatment. Values in diagonal line in the square brackets are surface under the cumulative ranking curve area; percentage probability of being best treatment.

antibiotic groups. A sensitivity analysis by excluding one study with highest complicated appendicitis did not change the results comparing with overall pooling. However, proper adjusting for this effect should be better analysis but this is required raw data.

Conclusion

Our evidence suggests that the use of antibiotics for treating uncomplicated appendicitis would result in about 12%–32% lower treatment success at 1 year than appendectomy but about 23%–86% fewer complications. 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 whereas Beta-lac and Cep + Met were ranked first and second in lowest complications. Evidences about benefits and risks for taking antibiotics or appendectomy should be provided to patients to properly choose their optimal course of actions with physicians. Further large scale RCTs should be conducted alongside economic evaluations.

Author contributions

Napaphat Poprom: Conceived the study, designed the study, data collection, analyzed the data, drafted the manuscript.

Pawin Numthavaj and Ammarin Thakkinstian: Supervised the conduct of the study, designed the study, data collection.

Chumpon Wilasrusmee: Designed the study, data collection.

Sasivimol Rattanasiri: Managed the data, including quality control.

Ammarin Thakkinstian, John Attia, and Mark McEvoy: Provided statistical advice on study design and analyzed the data.

All authors contributed substantially to its revision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.10.009.

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