Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials.

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CRD summary
The authors concluded that antibiotics could be used safely and effectively as primary treatment for uncomplicated acute appendicitis. Although based on a small number of trials, this was a well-conducted review. The authors’ conclusion reflects the evidence presented and seems reliable.

Authors’ objectives
To compare the safety and efficacy of antibiotic treatment versus appendicectomy for treatment of uncomplicated acute appendicitis.

Searching
MEDLINE, EMBASE and the Cochrane Library databases were searched with no language restrictions up to December 2011; search terms were reported. Manual searches were conducted using the 'related article' function of the electronic databases, and in bibliographies of randomised controlled trials (RCTs), meta-analyses and systematic reviews identified in the original search.

Study selection
Eligible studies were RCTs that compared antibiotic treatment versus appendicectomy for uncomplicated acute appendicitis in adults. The primary outcome was complications relevant to the condition (such as wound infection, incidence of perforated appendicitis or peritonitis). The main secondary outcomes were length of hospital stay, readmissions, and treatment efficacy. Eligible trials had to include at least two of the pre-specified outcomes. Non-randomised studies, retrospective studies, case series, and studies reporting outcomes for patients with complicated appendicitis were excluded.

In included trials, the mean age of patients ranged from 27 to 38 years (where reported). Diagnosed or suspected uncomplicated acute appendicitis was indicated via computed tomography, ultrasonography, gynaecological examination, laboratory tests, clinical signs (not stated), positive history, increased white blood cell counts, and high C reactive protein levels. Antibiotics administered were amoxicillin plus clavulanic acid, cefotaxime, ciprofloxacin, metronidazole, ofloxacin, and tinidazole. Doses and regimens varied, including antibiotics administered postoperatively. Most surgery was conducted using open or laparoscopic techniques.

Two reviewers independently selected studies for inclusion; discrepancies were resolved by discussion with a third reviewer.

Assessment of study quality
Randomisation method, allocation concealment, blinding, drop-outs and withdrawal description, intention-to-treat analysis, and follow-up duration were assessed as indicators of methodological quality. Overall quality of evidence for each outcome was assessed using the Cochrane Collaboration's GRADE (Grades of Recommendation Assessment, Development and Evaluation) tool. Trials were graded as very low, low, moderate, or high.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
The number of complications (perforated or gangrenous appendicitis, or peritonitis and wound infection) was extracted from each trial to calculate risk ratios (RRs) with 95% confidence intervals (CIs). Mean length of hospital stay was extracted to calculate mean differences (MDs) with 95% confidence intervals. Intention-to-treat data were extracted, where possible. Numbers of patients were extracted to demonstrate successful treatment with antibiotics or appendicectomy. The effects of antibiotics or appendicectomy on complications and recurrences were reported as secondary indicators of treatment efficacy.
Two reviewers independently extracted the data.

**Methods of synthesis**

Meta-analyses of risk ratios for complications and for risk of complicated appendicitis were conducted using the Mantel-Haenszel method. Mean differences for length of hospital stay were pooled using the inverse variance method. All meta-analyses were estimated using 95% confidence intervals. Heterogeneity was assessed using $\chi^2$ and $I^2$. Use of a fixed-effect model was proposed in the absence of statistical heterogeneity, otherwise a random-effects model was applied.

A sensitivity analysis for complications was conducted to assess whether treatment outcome was influenced by differences in antibiotic regimen. Sensitivity analyses for complications, length of hospital stay, and risk of complicated appendicitis were conducted following removal of one trial demonstrating crossover of patients.

A funnel plot was used to assess publication bias.

**Results of the review**

Four trials were included in the review (900 patients). The total number of patients per trial ranged from 40 to 369.

Randomisation methods were reported in three trials. Allocation concealment was described by two trials. Withdrawals/drop-outs were reported in three trials. None of the trials were blinded. Length of follow-up ranged from 10 days to one year. Median follow-up in all trials was one year. Overall GRADE criteria suggested low (for risk of complicated appendicitis) to moderate (for complications and length of hospital stay) quality of evidence.

A statistically significant relative risk reduction of 31% for complications was observed favouring antibiotic treatment over appendicectomy (RR 0.69, 95% CI 0.54 to 0.89; four trials; $I^2=0\%$). The result remained statistically significant when a trial with patient crossover was excluded (RR 0.61, 95% CI 0.40 to 0.92; three trials; $I^2=0\%$).

Findings from meta-analyses on length of hospital stay and risk of complicated appendicitis were statistically non-significant and demonstrated high statistical heterogeneity, even when the trial with patient crossover was removed ($I^2$ values ranged from 48% to 82%). Results for these meta-analyses and other secondary outcomes were reported in the paper. The number of patients successfully treated with antibiotics ranged from 41% to 76%.

No statistically significant differences for complications were observed between trials that administered cefuroxime plus metronidazole or tinidazole versus those that administered amoxicillin plus clavulanic acid (data not shown).

The funnel plot (data not shown) indicated risk of publication bias for the reporting of complications.

**Authors’ conclusions**

Antibiotics could be used safely and effectively as primary treatment for uncomplicated acute appendicitis.

**CRD commentary**

The aim of the review was clearly stated; the inclusion/exclusion criteria seemed replicable. Relevant databases were searched. Additional literature was identified by manual searches. There were no language restrictions, which meant that language bias was unlikely. A funnel plot showed that publication bias for complications was a possibility. Screening and data extraction were performed independently by two reviewers, which reduced the risk of reviewer error and bias.

The quality assessment criteria were appropriate for the included study designs, but the process of assessment was unclear. The meta-analyses and sensitivity analyses appeared to have been conducted appropriately for the data presented and were well-reported. Variability among the included trial characteristics potentially impacted on the generalisability of the findings.

This was a well-conducted review, although based on a small number of trials. The authors’ conclusion reflects the evidence presented and seems reliable.

**Implications of the review for practice and research**
Practice: The authors stated that antibiotics should be considered as the initial treatment option for acute uncomplicated appendicitis. Careful observation for perforation in patients with diagnosed or suspected uncomplicated appendicitis was suggested; early appendicectomy remained the 'gold standard' for treating those with clear signs of peritonitis or perforation.

Research: The authors stated that an early trial to evaluate antibiotics as an initial treatment option for uncomplicated appendicitis should be considered. Further investigation was required to study whether perforated and non-perforated appendicitis had different patterns and pathological processes.

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