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Short-Course Versus Long-Course Antibiotic Therapy For Complicated Appendicitis: A Meta-analysis

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Objective: To compare the efficacy of short-course versus long-course antibiotic therapy among patients undergoing appendectomy for complicated appendicitis.

Methods: The authors conducted an electronic search of PubMed, Cochrane Library, and EBSCOHost for studies from 2000 to January, 2000 to September, 2018 comparing short-course versus long-course antibiotic therapy in adults undergoing appendectomy for complicated appendicitis. The outcomes considered were the incidence of superficial surgical site infection and intra-abdominal abscess, and duration of hospital stay. Meta-analysis was performed using Review Manager software.

Results: A total of 360 patients in two studies were analyzed. Superficial surgical site infection was identified in 5 out of 123 patients in the short-course antibiotic group (4%), and 5 out of 237 patients in the long-course antibiotic group (2.1%) (95% CI 0.38, 5.51, p=0.58). There was a decrease in the incidence of intra-abdominal abscess in the short-course antibiotic group (6.5%), but the difference was not statistically significant (95% CI 0.32, 1.77, p=0.52). The duration of hospital stay was significantly less in the short-course antibiotic group (3.95 days) compared to the long-course antibiotic group (4.6 days) (95% CI -0.66, -0.21; p<0.001).

Conclusion: No difference between the <5-day and ≥5-day antibiotic course in terms of surgical site infection and intra-abdominal abscess was detected. However, the hospital stay of the <5-day group was shorter.

Keywords: Surgical wound infection, anti-bacterial agents, length of stay, appendectomy, abdominal abscess

Acute appendicitis is one of the most common diseases requiring surgical intervention. Appendicitis may be uncomplicated, which encompasses the congestive, suppurative, and phlegmonous types; or complicated, which includes the gangrenous and perforated type with peritonitis or peri-appendiceal abscess.[1] Appendectomy is the standard treatment for both classifications.

The incidence of post-operative incisional surgical site infection and intra- abdominal abscess (organ/space surgical site infection) is directly related to the amount of gross contamination to the wound and peritoneal cavity intra-operatively.[2] The use of perioperative antibiotics has been shown to decrease the incidence of these two complications.[1,3] The administration of a single dose of intravenous antibiotic prophylaxis is recommended for uncomplicated appendicitis.[1,3-5] However, various single and combination antibiotic therapies with different durations have been recommended worldwide by various surgical infection societies for complicated appendicitis.[3,6-9] While the guidelines by the Infectious Diseases Society of America and the Surgical Infection Society both had recommend limiting the duration of post-operative antibiotics for complicated intra-abdominal infections to 4 to 7 days[10], several studies have shown that there are practitioners who extend their antibiotic use to 10 to 14 days.[11,12] The Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial provided evidence that a fixed short-course duration of four days antibiotic treatment resulted in outcomes similar to those of a longer course.[13] Furthermore, shorter duration of antibiotic use is associated with decreased emergence of bacterial antibiotic resistance, lesser risk of toxicity, and lower cost of treatment. Currently, there is no consensus among surgeons on the duration of antibiotics for complicated appendicitis.

The general objective of this meta-analysis was to compare the efficacy of short-course (less than 5 days)

versus long-course (5 days or more) antibiotic therapy among adult patients undergoing appendectomy for complicated appendicitis. Specifically, in these two groups, the authors wanted to compare the incidence of incisional surgical site infections, the incidence of organ/space surgical site infections (intra-abdominal abscess), and the duration of hospital stay.

Methods

Randomized controlled trials or cohort studies that compared the incidence of incisional and organ/space surgical site infection, and duration of hospital stay among patients given antibiotics for less than 5 days with those given antibiotics for 5 days or more after undergoing appendectomy for complicated appendicitis were considered.

The review included studies where adult patients undergoing appendectomy for complicated appendicitis received single or combination antibiotic regimens for less than 5 days, or for 5 days or more.

Studies were considered if they used single or combination antibiotic regimens given for less than 5 days, or for 5 days or more.

Studies were considered if any one of the following clinical outcomes were studied:

1. Incidence of superficial surgical site infection
2. Incidence of organ/space surgical site infection (intra-abdominal abscess)
3. Duration of hospital stay

Search Strategy

All studies – randomized controlled trials or cohort studies - comparing the outcomes of short-course antibiotic therapy versus long-course antibiotic therapy after appendectomy for complicated appendicitis were identified by conducting an electronic search of the databases of PubMed, Cochrane Library, and EBSCOHost, using the following search terms: antibiotic duration, short-course antibiotic, long-course antibiotic, complicated appendicitis, and perforated appendicitis. Only studies in English, published from January 2000 to September 2018, with available full text were considered for this study.

Methods of the Review

All potential articles were screened for eligibility according to the criteria specified in the research protocol. Three reviewers extracted the data from the studies and recorded the data on a standardized data sheet. The third reviewer served as the arbiter to resolve all discrepancies. The quality of included studies was assessed independently on the following parameters based on the Cochrane Handbook for Systematic Reviews of Interventions: random sequence generation, allocation concealment, blinding of the patient, blinding of the observer, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Statistical Analysis

The software RevMan Version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. The risk ratio (RR) with 95% confidence interval was calculated for dichotomous outcomes and the mean difference (MD) with 95% CI for continuous outcomes. Statistical heterogeneity was investigated by inspecting the Forest plot and I^2 statistic. An $I^2 < 25\%$ was considered to indicate low heterogeneity and an $I^2 > 75\%$ to indicate high heterogeneity. Where heterogeneity remained unexplained, the random-effects model was to be applied. The Cochrane Collaboration tool was used for assessing risk of bias in design, conduct, analysis, and reporting.

Results

A total of fifty studies were identified after the search, and the abstracts of these articles were reviewed. Only five full text articles were found to be pertinent to the review after methodological assessment (1 RCT[14], 4 cohort studies[8,9,15,16]). Figure 1 shows the process of identification, screening, and inclusion of studies in this systematic review.

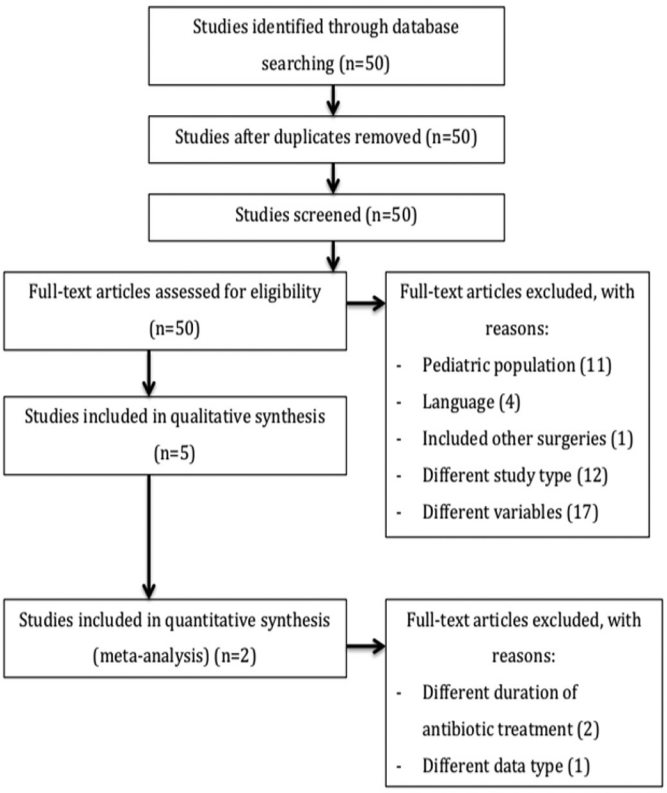

Figure 1. QUORUM statement flow diagram

Two studies with a total of 360 patients were included in this systematic review with pooling of results. All studies compared the use of short-course (<5 days) antibiotic therapy with long-course (≥ 5 days) antibiotic therapy after appendectomy for complicated appendicitis. The studies are summarized in Table 1. Assessment of quality according to the Cochrane Collaboration's tool for assessing risk of bias for RCT is reported in Figures 2 and 3. The blank spaces in the risk of bias assessment reflect an unclear risk for the particular item.

Incidence of Superficial Surgical Site Infection

Studies by both Taylor[14] and van Rossem[16] demonstrated no significant difference in the incidence of incisional surgical site infection between the short-course and long-course antibiotics groups. Wound infection was identified in 5 (4%) out of 123 patients in the short-course antibiotic group, and in 5 (2.1%) out of 237 patients in the long-course antibiotic group. The effects were homogenous (I^2=0%). The fixed effects model showed a RR of 1.46, but this was not statistically significant (95% CI: 0.38, 5.51, p=0.58), (Figure 4).

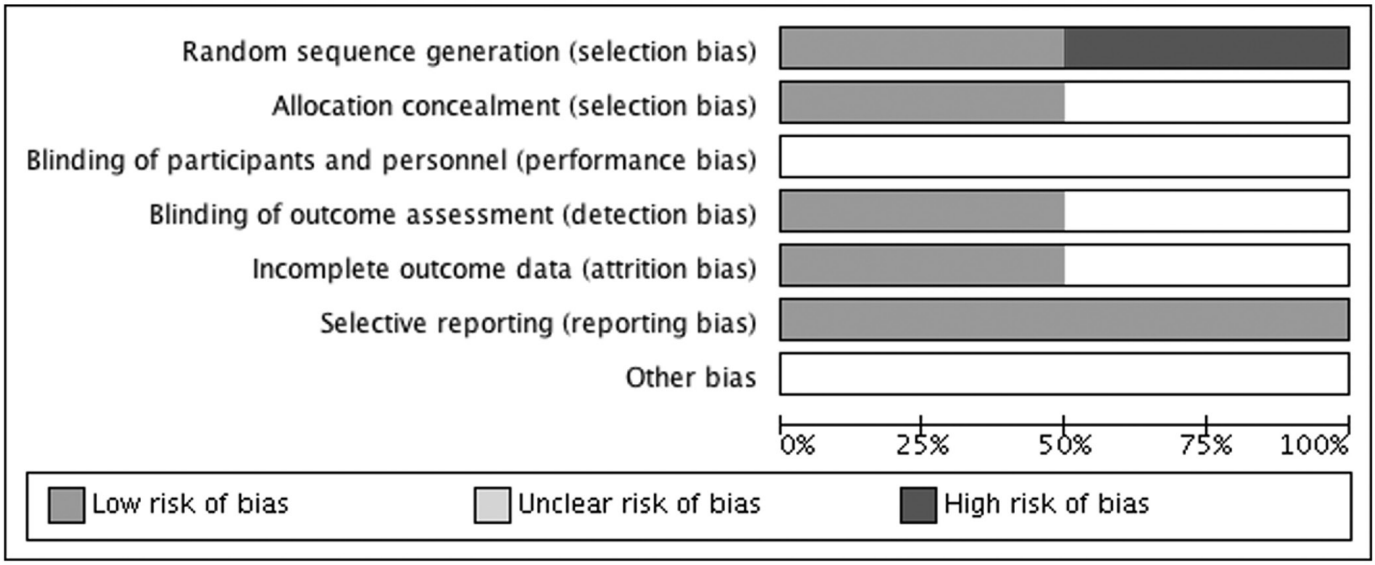

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

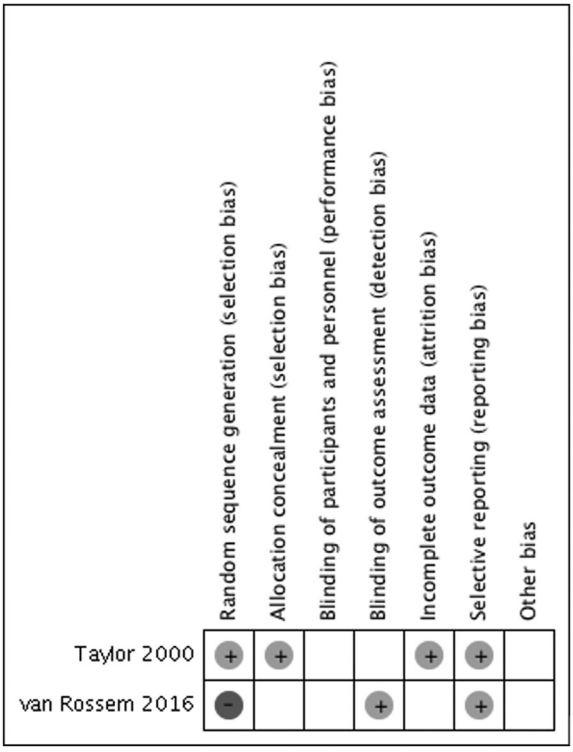

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Incidence of Organ/Space Surgical Site Infection (Intra-Abdominal Abscess)

There was a decrease in the incidence of intra-abdominal abscess in the short-course antibiotic group (6.5% vs 8.9%), but this difference failed to reach statistical significance (95% CI: 0.32, 1.77, p=0.52). The measured effects were homogenous (I^2=0%). The fixed effects model showed a RR=0.76 as seen in Figure 5.

Duration of Hospital Stay

The duration of hospital stay was significantly less in the short-course antibiotic group (3.95 days) compared to the long-course antibiotic group (4.6 days). The fixed effect model was used giving an overall mean difference of -0.44 (95% CI: -0.66, -0.21; p=0.0001). (Figure 6)

Discussion

Evidence-based guidelines for antibiotic treatment of complicated appendicitis recommend the administration of antibiotics for 5-7 days after surgery to reduced wound

Table 1. Summary of the characteristics of the studies in the systematic review.

Authors	Population	Intervention	Control	Outcome	Methodology
Taylor et al, 2000	97 patients with intra-operative findings of gangrenous or perforated appendicitis. Year: March 1996-March1998	No minimum IV antibiotic treatment (pre-operative ampicillin/sulbactam, postoperative cephalexin)	Minimum 5 days IV antibiotic treatment	- incidence of wound infections - incidence of intra-abdominal abscess - duration of hospital stay	Randomized controlled trial
Van Rossem et al, 2016	266 patients who underwent laparoscopic appendectomy for acute complicated appendicitis. Year: July 31, 2014-June 1, 2015	Treatment with antibiotics for 3 days (antibiotic not identified)	Treatment with antibiotics for 5 days	- incidence of wound infections - incidence of intra-abdominal abscess - duration of hospital stay	Prospective cohort study

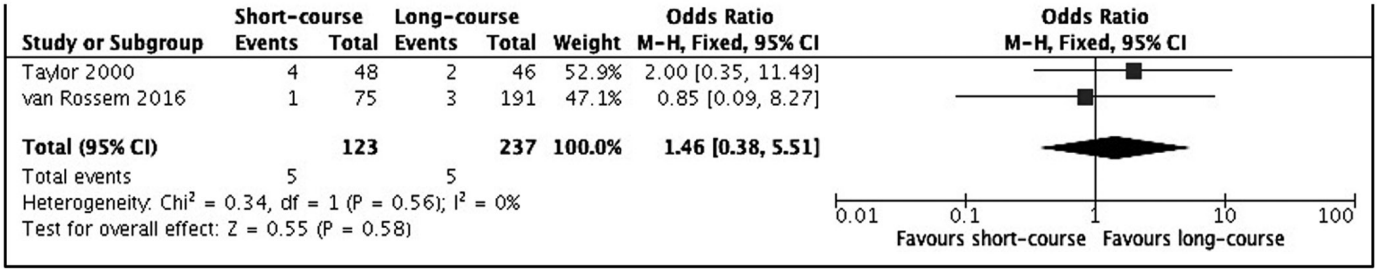

Figure 4. Incidence of incisional surgical site infection after short-course and long-course antibiotic therapy following appendectomy for complicated appendicitis, showing no statistical advantage of long-course therapy over short course therapy (p=0.58).

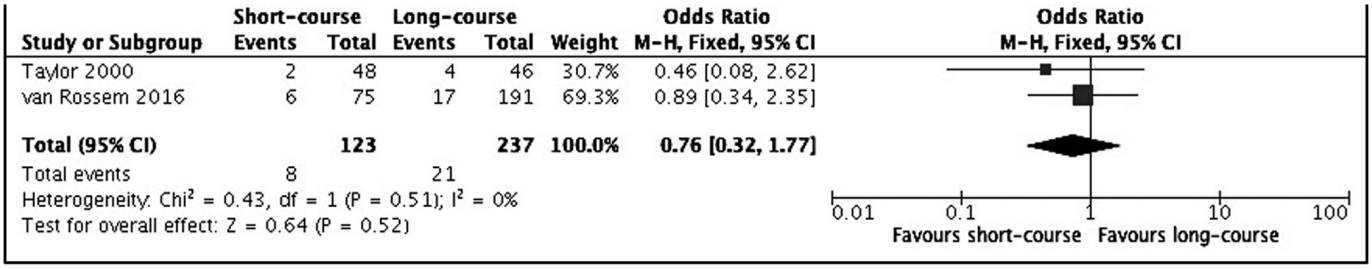

Figure 5. Incidence of intra-abdominal abscess after short-course and long-course antibiotic therapy following appendectomy for complicated appendicitis, showing no statistical advantage of long-course therapy over short-course therapy (p=0.52).

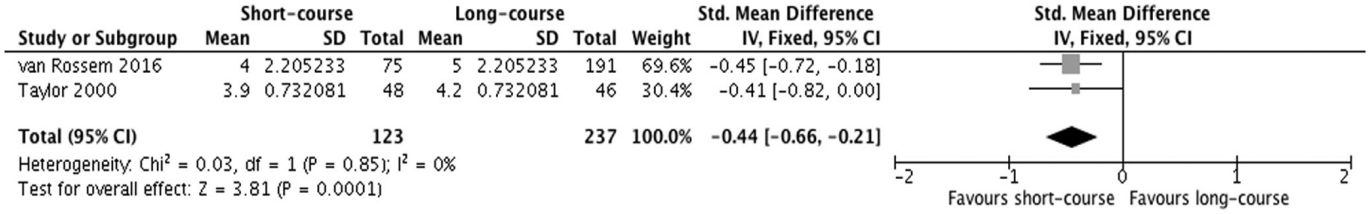

Figure 6. Duration of hospital stay after short-course and long-course antibiotic therapy following appendectomy for complicated appendicitis, showing statistical advantage of short-course therapy over long-course therapy (p=0.0001).

and organ-space infections.[1-17] Although variability exist on the timing of sequential therapy, most studies showed that after at least 24 hours of intravenous antibiotic therapy, shifting to oral antibiotic therapy is safe once the patient has improvement in clinical parameters such as absence of fever, decreasing leukocytosis, and return of normal gastrointestinal function.[1,2] However, a study on shortened antibiotic treatment showed no significant difference in infectious complications between a two-day course of antibiotic treatment and a four-day course of antibiotic treatment among patients with complicated intra-abdominal infections after their index source-control procedure.[13] And so, the question is raised, "Does a longer antibiotic treatment reduce post-operative infection rate in patients who underwent appendectomy for complicated appendicitis?"

Several studies have demonstrated that the administration of antibiotics post-operatively reduces post-surgical infectious complications, and subsequently, a shortened duration of hospital stay.[18] A study by Smith,

et al. demonstrated that antibiotic therapy less than seven days after source control among critically-ill patients with complicated intra-abdominal infections resulted in significantly less treatment failures (composite of recurrent complicated intra- abdominal infection, secondary extra-abdominal infection, and/or in-hospital mortality from any cause) compared to patients who had received fourteen days of antimicrobial therapy. In addition, a significantly shortened ICU and hospital stay for those who had received the short-course antibiotic therapy was reported.[19]

This meta-analysis showed trends toward a decrease in the incidence of incisional surgical site infection after long-course antibiotic therapy and a decrease in intra-abdominal abscess after the use of short-course antibiotic therapy, however the measured effects was not statistically significant. This is in concordance with other published studies. The study of van Rossem, et al, reported that three days of antibiotic therapy is as effective as five days in preventing infectious complications.[9] They noted that majority of patients who had developed an intra-abdominal abscess after prolonged antibiotic therapy had a pre-operative diagnosis of perforated appendicitis. Park, et al. conducted a study among patients who underwent laparoscopic appendectomy for complicated appendicitis, and reported that there was no difference in surgical site infection rates between the group who had received various antibiotic regimens (triple-agent therapy covering gram-positive, gram-negative, and anaerobic organisms) for a prolonged duration (10 days) and the group who received a standardized drug protocol (Cefuroxime and Metronidazole) for 5 days.[8] A study by Hughes, et al.[15] showed that the length of antibiotic course (≤5 days versus >5 days) was not associated with a significant difference in the incidence of intra-abdominal abscess after appendectomy.

This study demonstrated that the duration of hospital stay was significantly less in the short-course antibiotic group compared to the long-course antibiotic group, which is consistent with findings of several cohort studies.[8,9] While this difference is statistically significant (p=0.0001), it is not clinically significant (3.95 days vs 4.6 days). Park, et al. also indicated higher medical costs for the long-course antibiotic group, owing to the prolonged duration of antibiotic use as well as the expense of the various antibiotic regimens.[8] The studies in this systematic review did not perform a cost analysis; however, a lower cost may be expected with a short-course antibiotic regimen compared with a longer course of the same regimen.

Available data on duration of antibiotic treatment is limited, with only 1 RCT available.[14] The limited number of studies also restricted the analysis applicable to the data; fixed-effect and random-effect models yielded very similar results for each outcome. Although there are a number of studies looking into the most cost-effective duration for antibiotic therapy for complicated appendicitis, the studies are not standardized in terms of the duration for antimicrobial treatment.[8] There is a need for more studies to be done with a standardized duration of antibiotic therapy in order to come up with a stronger recommendation for this practice.

Conclusion

The results indicate that in complicated appendicitis, there is no difference between the <5-day and ≥5-day post operative antibiotic courses in terms of the incidence of surgical site infection and intra-abdominal abscess. The hospital stay of the <5-day group was shorter but the difference is not significant clinically.

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