



Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee Systematic Review[☆]

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Clinical Trials Committee

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Abstract

Objective: The aim of the study was to review evidence-based data regarding the use of antibiotics for the treatment of appendicitis in children.

Data Source: Data were obtained from PubMed, MEDLINE, and citation review.

Study Selection: We conducted a literature search using “appendicitis” combined with “antibiotics” with children as the target patient population. Studies were selected based on relevance for the following questions:

- (1) What perioperative antibiotics should be used for pediatric patients with nonperforated appendicitis?
- (2) For patients with perforated appendicitis treated with appendectomy:
 - a. What perioperative intravenous antibiotics should be used?
 - b. How long should perioperative intravenous antibiotics be used?
 - c. Should oral antibiotics be used?
- (3) For patients with perforated appendicitis treated with initial nonoperative management, what antibiotics should be used in the initial management?

Results: Children with nonperforated appendicitis should receive preoperative, broad-spectrum antibiotics. In children with perforated appendicitis who had undergone appendectomy, intravenous antibiotic duration should be based on clinical criteria. Furthermore, broad-spectrum, single, or double agent therapy is as equally efficacious as but is more cost-effective than triple agent therapy. If

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intravenous antibiotics are administered for less than 5 days, oral antibiotics should be administered for a total antibiotic course of 7 days. For children with perforated appendicitis who did not initially undergo an appendectomy, the duration of broad-spectrum, intravenous antibiotics should be based on clinical symptoms.

Conclusions: Current evidence supports the use of guidelines as described above for antibiotic therapy in children with acute and perforated appendicitis.

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Appendicitis is the most common surgical emergency in the pediatric population. Despite the widespread prevalence of the disease, there is little consensus regarding the diagnosis and management of appendicitis. In 2000, a survey of all members of the American Pediatric Surgical Association demonstrated controversy in virtually every aspect of the management of appendicitis [1]. With respect to antibiotic therapy, there was considerable variability in the choice, duration, and route of administration of antibiotics for both acute and perforated appendicitis. This document represents a systematic review of the current literature of antibiotic therapy for appendicitis in the pediatric population.

1. Material and methods

PubMed and other databases of the English literature (up to August 2009) were analyzed. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and the HTA Database were used as well. Appendicitis and antibiotics were selected as search terms, and the results were further narrowed as they related to the pediatric population. Studies were selected based on relevance for the following questions:

- (1) What perioperative antibiotics should be used for pediatric patients with nonperforated appendicitis?
- (2) For patients with perforated appendicitis treated with appendectomy:
 - a. What perioperative intravenous (IV) antibiotics should be used?
 - b. How long should perioperative IV antibiotics be used?
 - c. Should oral antibiotics be used?
- (3) For patients with perforated appendicitis treated with initial nonoperative management, what antibiotics should be used in the initial management?

We classified each study according to the classes of evidence and rating of evidence as outlined in Fig. 1 [2]. Once guidelines were established, grades were assigned based on the strength of the studies supporting the recommendation [3]. Overall, 126 studies were selected and reviewed. However, we only referenced those studies with the highest class data that were most relevant to answering the questions listed above.

2. Results

2.1. Acute appendicitis

2.1.1. Question 1: What perioperative antibiotics should be used for pediatric patients with nonperforated appendicitis?

In patients with nonperforated appendicitis, there is strong evidence that children should receive preoperative broad-spectrum antibiotics (Grade A). A Cochrane Database review looking at both adults and children support that a single dose of broad-spectrum antibiotics, given preoperatively is effective in decreasing wound infection and abscess formation [4]. This meta-analysis demonstrated that preoperative antibiotics significantly decreased the risk of wound infection and postoperative abscess compared to placebo. The studies that were reviewed used different antibiotics, including cefoxitin, piperacillin/tazobactam, and others (Table 1). This meta-analysis did include both adult and pediatric patients. There was no evidence supporting the use of a second dose of antibiotic in the postoperative period.

2.2. Perforated appendicitis treated with appendectomy

2.2.1. Question 2a: What perioperative antibiotics should be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

Patients with perforated appendicitis require antibiotics. Traditionally, “triple antibiotics” covering Gram-positive, Gram-negative, and anaerobic bacteria were administered to patients with perforated appendicitis for as long as 10 days [5]. However, newer antibiotics may decrease the number of days needed for antimicrobial therapy, the total number of doses required, and the side effects of therapy. There are several studies amounting to evidence (Grade B) that broad-spectrum, single, or double agent therapy is as effective as and more cost-effective than triple agent therapy [6-9]. A prospective, randomized trial conducted by St Peter et al [6] showed single daily dosing of ceftriaxone and metronidazole was more efficient, cost-effective, and had similar results compared to triple antibiotics.

A retrospective study showed piperacillin-tazobactam was more cost-effective and had similar results compared to triple antibiotics in patients with perforated appendicitis [7]. A

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ANTIBIOTIC USE FOR APPENDICITIS

What perioperative antibiotics should be used for pediatric patients with non-perforated appendicitis?

Grade A Evidence: Children with non-perforated appendicitis should receive preoperative, broad-spectrum antibiotics

What perioperative antibiotics should be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

Grade B Evidence: Broad-spectrum, single or double agent therapy is as effective as and more cost-effective than triple agent therapy

How long should perioperative intravenous antibiotics be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

Grade B Evidence: The duration of intravenous antibiotics should be based on clinical criteria, such as fever, pain, return of bowel function, and WBC.

Should oral antibiotics be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

Grade B Evidence: If IV antibiotics are administered for less than 5 days, then oral antibiotics should be administered for a total antibiotic course of 7 days.

What perioperative antibiotics should be used for patients who will undergo interval appendectomy?

Grade D Evidence: The duration of intravenous antibiotics given preoperatively should be based on clinical criteria, such as fever, pain, return of bowel function, and WBC count. Broad-spectrum, single or double agent therapy is as effective as and more cost-effective than triple agent therapy.

Classes of Evidence <i>(Surgical Infections 3:161-173, 2002)</i>	Rating Scales of Evidence <i>(Surgical Infections 7:275-303, 2006)</i>
<ul style="list-style-type: none"> I Prospective randomized controlled trials or meta-analysis of such trials II Prospective studies without randomization or other studies in which data were collected prospectively, and retrospective analyses based on clearly reliable data. These include observational studies, cohort studies, prevalence studies, and retrospective case control studies III Uncontrolled studies using retrospective data, such as clinical series or case reviews, and expert opinion 	<ul style="list-style-type: none"> A ≥ 2 large class I studies B 1 large class I study C Small, randomized trials with uncertain results D ≥ 1 non-randomized trial with controls E Expert opinion, case reports, uncontrolled studies

Fig. 1 Summary of systematic review for use of antibiotics for appendicitis in the pediatric population.

Table 1 Summary of Cochran Database Review regarding use of antibiotics for nonruptured appendicitis

	Odds ratio	95% confidence interval
Wound infection		
Placebo (n = 2707)	Reference	Reference
Antibiotics (n = 2610)	0.37	0.30-0.46
Abscess		
Placebo (n = 1535)	Reference	Reference
Antibiotics (n = 1433)	0.46	0.33-0.94

prospective trial compared triple antibiotics to piperacillin-tazobactam administered for 10 days showed outcomes that are similar to the triple antibiotic therapy described by Lund and Murphy [5]. Ciftci et al [9] prospectively compared piperacillin, ceftriaxone, ornidazole, and triple antibiotics, again with no statistically significant differences in infectious outcomes.

Comparing the cost of different antibiotic regimens is difficult to assess as most of the cost will be because of the length of hospitalization and morbidity rate. However, because studies have shown similar efficacy with respect to morbidity and length of hospitalization [6-9], then we would expect the overall costs for the different regimens to be similar. When directly comparing the cost of the antibiotics, inpatient antibiotic charges for ceftriaxone and metronidazole was significantly less than for triple antibiotics (\$1413 ± \$782 vs \$1940 ± \$633; $P < .001$) [6].

2.2.2. Question 2b: How long should perioperative IV antibiotics be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

The duration of intravenous antibiotics administered for perforated antibiotics had traditionally been 7 or 10 days. However, the severity of peritonitis and clinical illness in patients with perforated appendicitis vary. Therefore, an empiric length of time for antibiotics may result in many patients receiving IV antibiotics for a longer time than necessary. There is Grade B evidence that the length of administration of IV antibiotics should be based on clinical criteria, such as fever, pain, return of bowel function, and white blood cell (WBC) count [10,11].

2.2.3. Question 2c: Should oral antibiotics be used for pediatric patients with perforated appendicitis who are undergoing appendectomy?

Fraser et al [11] conducted a well-powered, single-institution prospective, randomized trial that showed that

when patients are able to tolerate a regular diet, completing the course of antibiotics orally had similar results compared to a minimum 5-day course of IV antibiotics (Grade B).

2.3. Perforated appendicitis treated with initial nonoperative management

2.3.1. Question 3. What antibiotics should be administered for patients during their initial management who will undergo subsequent interval appendectomy?

Interval appendectomies have been used increasingly in patients who present with ruptured appendicitis, allowing inflammation to decrease before surgical intervention. There are several studies regarding type and duration of antibiotics for this circumstance, but the evidence can only be described as Grade D [11-15]. The duration of intravenous antibiotics should be based on clinical criteria, such as fever, pain, return of bowel function, and WBC count [16,17]. Broad-spectrum, single, or double agent therapy is as effective as and more cost-effective than triple agent therapy. A summary of the results from these studies is provided in Table 2.

3. Summary of recommendations

1. In patients with nonperforated appendicitis, there is strong evidence that children should receive preoperative broad-spectrum antibiotics (Grade A).
2. Broad-spectrum, single, or double agent therapy is as effective as and more cost-effective than triple agent therapy for the treatment of perforated appendicitis (Grade B).
3. The length of administration of IV antibiotics for children with perforated appendicitis should be based on clinical criteria, such as fever, pain, return of bowel function, and WBC count (Grade B).
4. In children with perforated appendicitis, a 5-day course of IV antibiotics is recommended. IV antibiotics are given initially, but completing the antibiotic course with oral antibiotics (total 7 days IV + oral) had similar results compared to a minimum 5-day course of IV antibiotics (Grade B).
5. The duration of administration of broad-spectrum IV antibiotics for nonoperative management of perforated appendicitis should be based on clinical criteria (Grade D).

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Table 2 Summary of studies describing use of antibiotics for patients who will undergo delayed (interval) appendectomy for ruptured appendicitis

IV antibiotics	Patients treated	Recurrence or failure
10-14 days (10, 11)	108	28 (26%)
Clinical criteria (12-15)	235	46 (20%)

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