

# Antibiotic Treatment in Complicated Appendicitis: Can It Be Optimized?

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**ABSTRACT** **Background:** The management of complicated appendicitis is inconclusive. Guidelines have not been established for the use of personalized antibiotic treatment.

**Objectives:** To investigate specific risk factors to consider during the initial first-choice antibiotic therapy in children with complicated appendicitis.

**Methods:** This study included all pediatric patients younger than 18 years of age who underwent a laparoscopic appendectomy during 2012–2022 at a single tertiary medical center.

**Results:** In total, 300 pediatric patients underwent laparoscopic appendectomy due to complicated appendicitis. The patients were treated with ceftriaxone + metronidazole (CM). For 57 (19%) patients, the empirical treatment was changed to tazobactam/piperacillin (TP) due to resistant bacteria or clinical deterioration. The presence of generalized peritonitis during surgery and C-reactive protein (CRP) levels above 20 mg/L at admission were identified as risk factors for changing the antibiotic regimen from CM to TP.

**Conclusions:** Generalized peritonitis and CRP > 20 gr/L were highly correlated with changing the antibiotic regimen to TP. For such patients, initial treatment with TP may result in clinical improvement and shorter hospitalization.

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**KEY WORDS:** complicated appendicitis, empirical antibiotic treatment, pediatric, peritonitis, resistant bacteria

Nevertheless, controversies remain regarding the specific antibiotic regimen for complicated appendicitis. Notably, a dual regimen consisting of ceftriaxone and metronidazole (CM) is prevalent in many hospitals due to advantages such as once daily dosing and low drug cost. In addition, CM may show less community antibiotic resistance. However, some physicians advocate the use of a broader spectrum regimen, such as tazobactam/piperacillin (TP). This treatment decreases abscess formation due to its anti-pseudomonal cover, although supporting literature is lacking [2].

While much research has compared PT to CM as the initial treatment for complicated appendicitis [3–7] to the best of our knowledge, whether antibiotic regimen should be based on a decision-making choice and on risk factors has not been addressed. In other words, can we predict, based on initial data, the more suitable regime for the patient, hence optimizing his or her clinical course?

In this study, we investigated specific risk factors that could guide us through the initial first-choice antibiotic therapy in children with complicated appendicitis.

## PATIENTS AND METHODS

### STUDY DESIGN

This retrospective cohort study included all pediatric patients who underwent laparoscopic appendectomy during 2012–2022 at Schneider Children's Medical Center of Israel, a tertiary medical center and who were diagnosed with complicated appendicitis.

Complicated appendicitis was defined by five presentations [8]. The first was gangrenous appendicitis, based on the surgeon's macroscopic evaluation during the procedure. The second was evidence of a perforated appendix during the surgery. The third was a gangrenous, perforated appendicitis, as evident by the combination of a macroscopic appearance of gangrenous appendicitis

Appendicitis is the most common surgical emergency in the pediatric population. Despite its prevalence, almost every aspect of the management, and specifically antibiotic therapy, remains controversial. In a systemic review, Lee et al. [1] described the traditional administration of a triple-antibiotics regimen covering gram-positive, gram-negative, and anaerobic bacteria, followed by dual therapy or monotherapy. The authors found that broad spectrum, single- or double-agent therapy was as effective as, and more cost-effective than, triple-agent therapy for treating perforated appendicitis.

with signs of perforation. Fourth was a peri-appendicular abscess, as evident by the presence of a walled-off peri-appendicular abscess. Fifth was diffuse peritonitis, as evident by signs of an inflamed peritoneum, either purulent or fecal peritonitis.

# ANTIBIOTIC REGIMEN

From 2012, a dual antibiotic regimen consisting of ceftriaxone and metronidazole (CM) was initiated in our department. According to our protocol, patients with complicated appendicitis were treated for at least 4 to 5 days with intravenous antibiotics, before discharge. The empirical antibiotic regimen was upgraded to TP if the clinical condition deteriorated or if drug-resistant bacteria was documented. Evidence of clinical deterioration included fever, leukocytosis, or the presence of intra-abdominal collections following surgery. Documentation of drug-resistant bacteria from intra-abdominal fluid included *Pseudomonas aeruginosa* or extended spectrum beta lactamase (ESBL) with incomplete clinical and laboratory resolution.

The antibiotic regimen was upgraded, as necessary, to TP. Notably, evidence of intra-abdominal fluid prompted sending cultures for microbiology analysis. In this study, we investigated differences in clinical characteristics and outcomes between patients who were upgraded to TP and patients who remained with empirical dual CM antibiotic treatment.

# DATA ACQUISITION AND ANALYSIS

The study was approved by our local institutional review board committee. All data were collected via the computerized hospitalization records for each patient. The data included age, sex, clinical presentation, laboratory results, and imaging findings. Operative data, including pathologic reports and postoperative outcomes, were also collected.

# STATISTICAL ANALYSIS

Baseline and studied variables were compared between patients who were upgraded to TP and patients who remained with empirical dual antibiotic treatment (CM). A Shapiro-Wilk test was performed for continuous variables to determine normal distribution. Accordingly, continuous variables were compared using the independent sample *t*-test or Mann-Whitney test, for normally distributed and non-normally distributed variables, respectively. Pearson chi-square test of independence or Fisher's exact test was performed for categorical variables, as appropriate. Following the univariate analysis, a multivariate logistic regression model was constructed to determine risk factors for antibiotic regimen upgrade. Statistical significance was considered as a 2-tailed *P*-value  $\leq 0.05$ .

# RESULTS

Overall, 300 patients with acute complicated appendicitis aged 2–18 years underwent laparoscopic appendectomy during 2012–2022. There was slight male predominance. The chief complaint, aside from right lower quadrant pain, was vomiting (65% of the patients). Following their surgery, all the patients were admitted to the pediatric surgery ward. The mean length of hospitalization was one week. Most of the patients had gangrenous appendicitis, and one-third of them (98) had macroscopic perforation of the appendix. Readmission occurred in 5.3% of the patients, mainly due to abdominal pain with or without fever, and elevated levels of white blood cells or C-reactive protein (CRP). All the patients recovered successfully. The patient characteristics are depicted in Table 1.

**Table 1.** Patient characteristics and preoperative data (N=300)

Characteristic	Value
Age in years, mean (median, range)	10.8 (11, 2.1–18)
Sex (male:female)	177:123 (59%/41%)
Preoperative white blood cell count (median, range)	16.28 (16, 2.3–36) cells/mm <sup>3</sup>
Preoperative CRP level, mean (median, range) mg/L	10.14 (6.8, 0.1–46) mg/L
<b>Clinical picture</b>	
Fever (%)	112 (37%)
Vomiting (%)	194 (65%)
Diarrhea (%)	35 (12%)
Days prior to admission with clinical symptoms (on average)	2 days
<b>Macroscopic findings during surgery</b>	
Gangrenous appendicitis (%)	142 (47%)
Perforated appendicitis (%)	54 (18%)
Gangrenous and perforated appendicitis (%)	44 (15%)
Periappendicular abscess (%)	28 (9%)
Peritonitis (%)	32 (11%)
Readmission (%)	16 (5.3%)

CRP = C-reactive protein

CHANGING THE ANTIBIOTIC REGIMEN

During the study period, all the patients were treated initially with empirical intravenous antibiotics according to our protocol. For 57 patients (19%), the empirical treatment was changed to TP 3–4 days following the surgery, and only following receipt of the bacteriology report.

Table 2. Patient characteristics according to antibiotic regimen

Characterization	Ceftriaxone + metronidazole (n=243)	Tazobactam/piperacillin (n=57)	P-value
Male sex	151 (62%)	26 (45%)	0.022
Mean age, years	11	9.5	0.01
Days prior to admission with clinical symptoms (mean)	2	3	0.0001
Fever	82 (34%)	30 (53%)	0.007
Vomiting	151 (62%)	43 (75%)	0.058
Diarrhea	22 (9%)	13 (23%)	0.003
Preoperative white blood cell count	16.4	15.6	0.29
Preoperative CRP level, gr/L	8.7	15.9	0.0001
Average length of hospitalization in days	6	12	0.001
Resistant bacteria in abdominal fluid	8 (3%)	35 (61%)	0.0001
Readmission	10 (4%)	6 (11%)	0.003
Macroscopic findings during surgery			
Gangrenous appendicitis	130 (53%)	12 (20%)	0.0004
Perforated appendicitis	39 (16%)	15 (26%)	0.52
Gangrenous and perforated appendicitis	38 (16%)	7 (12%)	0.522
Peri-appendicular abscess	20 (8%)	8 (14%)	0.175
Peritonitis	16 (7%)	16 (28%)	0.000001

CRP = C-reactive protein

Table 3. Multivariate analysis of risk factors for a change in antibiotic treatment

Characterization	Odds ratio	95% confidence interval	P-value
Male sex	0.4769	0.2521–0.9021	0.0228
Fever	1.4997	0.7836–2.8703	0.2385
Diarrhea	2.0717	0.8586–4.9989	0.1051
Peritonitis	4.2128	1.8161–9.7723	0.0008
CRP ≥ 20 gr/L	3.2932	1.5863–6.8365	0.0014

CRP = C-reactive protein

Among patients whose antibiotic regimen was changed to TP compared to those for whom it was not, the mean age was younger (9.5 years vs. 11 years. mean age) and a higher proportion was female (55% vs. 38%). Among the former compared to the latter, systemic symptoms (fever, diarrhea) were more common, and the duration of clinical symptoms prior to admission was longer. For the patients who received an antibiotic upgrade, compared to those who did not, the mean values were twofold: CRP level (15.9 vs. 8.7 mg/L) and of length of hospitalization (12 vs. 6 days).

A macroscopic finding of generalized peritonitis was also a risk factor for changing the antibiotic regimen. Drug-resistant bacteria was significantly more detected among patients who were treated with TP. This result was expected as the detection of resistant bacteria led to upgrading of the empirical antibiotic regimen. However, eight patients did not need such an upgrade due to complete resolution, as evident from improvements in their clinical and laboratory data.

Table 2 presents demographic and clinical characteristics according to the antibiotic regimen.

MULTIVARIATE ANALYSIS OF RISK FACTORS

The results of the multiple analysis are presented in Table 3. The presence of generalized peritonitis and CRP levels above 20 mg/L were identified as individual risk factors for changing the antibiotic regimen using logistic regression. In addition, male sex was found to be a protective individual risk factor against upgrading the antibiotic treatment. No major adverse events were considered to have resulted from the use of either antibiotic regimen.

DISCUSSION

The management of complicated appendicitis is still being debated. Issues such as the optimal antibiotic regimen and the duration of therapy remain without consensus [9].

Our research focused on patients with complicated appendicitis who were treated with dual therapy (CM) empirically. We found that for 19%, the antibiotics regime was shifted to TP. This shift was mainly due to resistant bacteria or clinical deterioration, including fever or intractable diarrhea due to intra-abdominal collections. These patients were younger, and the majority were females. They experienced systemic symptoms and for longer duration preoperatively, and their readmission rate was higher.

In addition, the patients whose antibiotic regimen was updated were hospitalized for twice as long as the patients who did not necessitate a change in antibiotics. In our study, we found correlations of the presence of generalized peritonitis and of CRP > 20 gr/L, with the need to change the antibiotic regimen to TP.

Several researchers have addressed the optimal antibiotic regimen for complicated appendicitis, with particular attention to increasing antibiotic resistance in *P. aeruginosa*. In 2013, the U.S. Centers for Disease Control and Prevention advocated judicious use of anti-pseudomonal antibiotics [10], although microbiologic evaluation of surgical specimens isolated *P. aeruginosa* in almost 15% of patients with perforated appendicitis [11]. Several studies [5,6] compared CM to TP to establish an optimal clinical outcome, while minimizing exposure to unnecessary broad spectrum antibiotic therapy. However, the comparison was simultaneous, and specific risk factors that could elucidate the preferred antibiotic regimen were not identified.

Notably, to the best of our knowledge, no study has addressed an antibiotic decision tree model initially, although numerous researchers have described optimal antibiotic treatment. Moreover, as there is no consensus of the optimal treatment, a choice of a specific antibiotic regime can potentially lead to resistant bacteria or to a narrower spectrum that could result in under-treatment. This finding highlights the importance of additional clinical, laboratory, and surgical findings that could facilitate better choice of the initial antibiotic regimen.

Two risk factors, the presence of generalized peritonitis and CRP > 20 gr/L, were highly correlated with the need to change the antibiotic regimen to TP. In other words, those patients necessitated the use of broader spectrum antibiotics, as they did not improve with CM as empirical antibiotics. Following our findings, we suggest examining a protocol that would implement TP initially to patients presenting with the identified features (i.e., general peritonitis or CRP > 20 gr/L). This protocol could yield clinical improvement and shorter length of hospitalization.

This study has several limitations due to its retrospective design. In addition, we did not compare the two regimens of antibiotics therapy (CM and TP). However, the large homogeneous cohort of patients were treated in the same manner over the decade, including the same method of surgery, the same empirical antibiotic choice of therapy, and the same detailed protocol.

## CONCLUSIONS

Specific, easily detected risk factors were identified for a change in antibiotic regimen for complicated appendicitis. The findings may contribute to implementation of more comprehensive and decision-based antibiotic therapy. This protocol may lead to clinical improvement and minimizing the length of hospitalization.

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