



Management and Microbiology of Perforated Appendicitis in Pediatric Patients: A 5-Year Retrospective Study

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ABSTRACT

Introduction: This study aims to assess the current epidemiology and microbiology of perforated appendicitis, how antibiotic choice and duration correlate with meaningful clinical outcomes, and whether serial white blood cell (WBC) counts provide clinical value.

Methods: Five-year retrospective cohort study, 2015–2019, among 333 consecutive children, ages 0–18 years, treated at St. Louis Children’s Hospital for perforated appendicitis. Main outcomes included length of stay (LOS), postoperative abscess formation, and readmission. Statistical analysis was performed with uni- and multi-variate analyses.

Results: Intra-abdominal cultures most commonly grew *Bacteroides fragilis* (52%) and *Escherichia coli* (50%). Patients who initially

received broad-spectrum antibiotics (meropenem, piperacillin-tazobactam, fourth-generation cephalosporins) for perforated appendicitis had greater rates of postoperative abscess formation (25% vs. 12%, $p < 0.01$) and LOS (7.0 vs. 5.7 days, $p < 0.01$). Similarly, antibiotics at time of discharge were associated with greater postoperative abscess formation (22% vs. 9%, $p < 0.01$) and LOS (6.4 vs. 5.6 days, $p = 0.02$). However, discharge with strictly oral antibiotics was not correlated with greater LOS, postoperative abscess formation, or readmission rates compared to discharge without antibiotics. Serial WBC counts had no predictive value for LOS, postoperative abscess formation, or readmission.

Conclusions: *Bacteroides fragilis* and *E. coli* were the most common intra-abdominal microbes for perforated appendicitis among our cohort. In non-critically ill children, the routine use of broad-spectrum antibiotics or continuation of antibiotics beyond discharge was not correlated with improved clinical outcomes. Additionally, WBC counts were not correlated with meaningful clinical outcomes.

Keywords: Antibiotic stewardship; Complicated appendicitis; Pediatric surgery

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Key Summary Points

Why carry out this study?

Appendicitis is among the most common surgical emergencies, and perforated appendicitis continues to be a source of morbidity with significant practice variation in management of these children

Our article uses an extensive 5-year retrospective experience to address common management questions: the utility of the white blood cell (WBC) count, use of broad- versus narrow-spectrum antibiotics, and practice of discharging patients home with antibiotics

What was learned from the study?

These data are important to show the WBC count, used to treat perforated appendicitis, is not reliable and lend further credence to the principal of treating the patient rather than the laboratory parameters

Furthermore, our article demonstrates that patients are over-treated with broad and lengthy antibiotic duration regimens with no patient benefit. Taken together, these data have important implications for a common pediatric problem

INTRODUCTION

Complicated appendicitis is one of the most common surgical emergencies in pediatrics, with the standard of care resting on the pillars of surgical resection and antibiotic treatment [1, 2]. While the surgical aspect is relatively well defined, laparoscopic or open appendectomy, the roles of bacterial cultures and antibiotics, including agent, duration, and route, are less clear. Review of the current literature

demonstrates discord over the utility of intraoperative cultures in guiding antibiotic decision making and preventing subsequent intraabdominal abscesses, the most common postoperative complication of perforated appendicitis [3, 4]. While the choice of antibiotics varies by surgeon and across institutions, the overall duration and coverage spectrum for perforated appendicitis has become shorter and more specific. Previous studies have shown antibiotic therapy consisting of metronidazole and a third-generation cephalosporin to be effective in the management for perforated appendicitis, although “broad-spectrum” antibiotics continue to be routinely used [5, 6]. Following surgery, postoperative complications are potentially worse among patients discharged home with intravenous antibiotics compared to oral antibiotics [7–9]. Additionally, the approach of discharging patients without home oral antibiotic courses has been validated in the setting of a normal white blood cell (WBC) count [10–13].

WBC trends are routinely used as a diagnostic aide in both the diagnosis and subsequent management of perforated appendicitis. Although an initial WBC may guide the diagnosis or exclusion of appendicitis, the predictive value and subsequent monitoring of serial WBCs remain questionable. One study of 44 pediatric patients with perforated appendicitis showed no significant difference in admission WBC among patients who later developed postoperative abscesses versus those who did not [14]. Furthermore, no patient developed an abscess if they were tolerating a regular diet by postoperative day 3. To this end, recent data suggest patients can be safely discharged home when clinically well (afebrile, tolerating a diet without nausea or emesis, pain controlled) without the need to check the WBC [15].

The objectives of this study were to: (1) describe the bacterial growth patterns observed in children with perforated appendicitis in a single large academic center; (2) determine whether there are correlations between antibiotic choice or duration and clinical outcomes in perforated appendicitis; (3) assess whether monitoring WBC correlates with meaningful clinical outcomes.

METHODS

Design, Setting, Participants

This study received approval from the Washington University in St. Louis institutional review board (IRB), ID #201908150. A retrospective cohort study was conducted among children, ages 0–18 years, treated at St. Louis Children’s Hospital (SLCH) for perforated appendicitis from 2015 to 2019. All cases admitted for appendectomy at SLCH during the study time frame were reviewed, and patients were included if the primary surgeon identified the appendix as being “perforated” in their operative findings at the time of removal ($N = 335$). Two patients were excluded. One patient had been admitted for several days at another hospital before transferring at the time of surgery, and records were limited. The other excluded patient had extensive comorbidities/underlying pathology that confounded their presentation and subsequent hospital course. After exclusions, 333 consecutive pediatric patients remained for consideration.

Exposures

Initial management type was at the discretion of the attending surgeon. Patients who had surgery as the initial management underwent open or laparoscopic appendectomy within 24 h of admission. In some situations, a preoperative drainage procedure was performed by the interventional radiology service, also within 24 h of admission. In general, these were patients who presented with prolonged symptoms (> 5 days of pain) as well as imaging demonstrating a mature abscess (rim-enhancing, drainable by interventional radiology). Medical therapy was defined as antibiotics only without intent for immediate intervention, either surgical or radiologic. In both of these latter scenarios, patients returned weeks later for interval appendectomy and rarely required overnight admission. Perforated appendicitis was defined as presence of intra-luminal contents outside of the bowel at time of surgery (as per the operative note) [16].

Three distinct types of intra-abdominal cultures were identified based on time of collection. Intraoperative cultures were collected at the time of appendectomy. Preoperative drainage cultures were obtained from interventional radiology drain collection prior to interval appendectomy. Postoperative abscess cultures were obtained from interventional radiology drain following identification of a postoperative intra-abdominal abscess, usually ≥ 5 days after initial appendectomy.

The initial antibiotic choice was defined as the preoperative antibiotics chosen by the surgical and medical teams at time of diagnosis. Broad-spectrum antibiotic coverage was defined as treatment with meropenem, piperacillin-tazobactam, and/or a fourth-generation cephalosporin. Narrow antibiotic coverage groups were exclusively treated with metronidazole plus a third-generation cephalosporin, most commonly ceftriaxone.

Admission and discharge WBC counts were evaluated, when available, for the patients in the study cohort. An admission WBC count ($N = 316$) was obtained either at a preceding institution or on arrival prior to the initial intervention, defined above. A discharge WBC count ($N = 301$) was only included in evaluation if it was obtained within 24 h prior to discharge.

Main Outcomes and Measures

Main outcome measures included length of stay (LOS) in days (determined by the number of midnights admitted), readmission within 30 days, postoperative abscess formation as defined by fluid collection requiring drainage as decided by the attending surgeon, and total days of antibiotic use.

Statistical Analysis

Univariable analysis was first performed using Fisher’s exact tests and chi-square analyses for binary outcomes. A two-sample *t*-test was used for continuous variables. A multivariable logistic regression was subsequently conducted to assess the impact of multiple exposures (age,

sex, race, admission WBC, and initial broad-spectrum antibiotic use) on postoperative abscess formation. The exposures of interest were chosen by the research team prior to performing the analysis. A p value < 0.05 was considered significant.

RESULTS

Of the 333 patients included in this study, 44% were female, 78% were Caucasian, and 16% were African American. Female patients had a shorter average LOS (5.5 vs. 6.4 days, $p < 0.01$) and shorter average antibiotic duration (9.7 vs. 11.2 days, $p = 0.04$), but no significant differences were present in postoperative abscess formation or readmission rate. African American patients had no significant difference in age, antibiotic duration, postoperative abscess formation, or readmission rate compared to Caucasian patients. However, African American patients did have a longer average LOS (7.0 vs. 5.7 days, $p = 0.02$). The mean age was 10.3 (SD 3.9) years (Table 1). The age group with the highest rate of postoperative abscesses was in children < 3 years old (Fig. 1).

The majority of patients, 89% ($N = 295$), with perforated appendicitis underwent a primary surgical intervention. The remaining patients were initially managed with either radiologic drainage ($N = 24$) or medical management ($N = 14$). The average patient in the surgical group was 2 years younger than those

in the preoperative drainage or medical management groups (10.1 vs. 12.1 vs. 12.8). The average total course of antibiotics was shortest in the surgical group (10.4 vs. 15.3 vs. 17.6) but the readmission rate was approximately the same among all groups (7–8%).

Preoperative drainage cultures were the most likely to show bacterial growth, with identifiable growth on 96% (25/26) of cultures, followed by 87% (40/46) growth on intraoperative cultures and 51% (25/49) growth on postoperative abscess cultures (Table 2). *Bacteroides fragilis* and *Escherichia coli* were the most prevalent bacteria isolated, occurring in 52% and 50%, respectively, of intra-abdominal cultures. *Pseudomonas aeruginosa* grew in 12% of cultures. Blood cultures had a positive growth rate of only 5% (3/60). In 11 cases, a patient had both an intraoperative surgical site culture and a postoperative abscess culture (Table 3). Among these 11 cases, 2 had identical culture profiles, both growing *E. coli* and *P. aeruginosa*, with one case also growing Viridans group streptococcus on both cultures. In seven cases, intraoperative cultures had positive bacterial growth but the postoperative abscess culture was sterile. In only one case was an additional pathogen identified on the postoperative abscess that was not present in the intraoperative culture; the patient grew *B. fragilis* and *E. coli* on intraoperative culture before growing *E. coli* and *P. aeruginosa* on postoperative abscess culture.

Patients who were treated initially with broad-spectrum antibiotics prior to surgery had significantly higher rates of postoperative abscess formation (25% vs. 12%, $p < 0.01$), longer average LOS (7.0 vs. 5.7, $p < 0.01$), and longer average antibiotic duration (13.5 vs. 10.4, $p < 0.01$), as seen in Table 4. There was no significant difference in rate of readmission (8% vs. 6%, $p = 0.61$). Among patients with an initial surgical management ($N = 295$), outcomes were compared between patients that were discharged home with antibiotics (PO, IV, or a combination) ($N = 180$) versus patients whose antibiotics were discontinued at time of discharge ($N = 115$). Patients discharged with home antibiotics had a significantly higher rate of postoperative abscess formation (22% vs. 9%, $p < 0.01$) and longer average total LOS (6.4 vs.

Table 1 Study population demographics

	Total population demographics
Average (standard deviation)	
Age (years)	10.3 (3.9)
Total length of stay (days)	6.0 (3.0)
Antibiotic duration (days)	10.5 (6.4)
Total (%)	
Postoperative abscess	52 (16%)
Readmission	23 (7%)

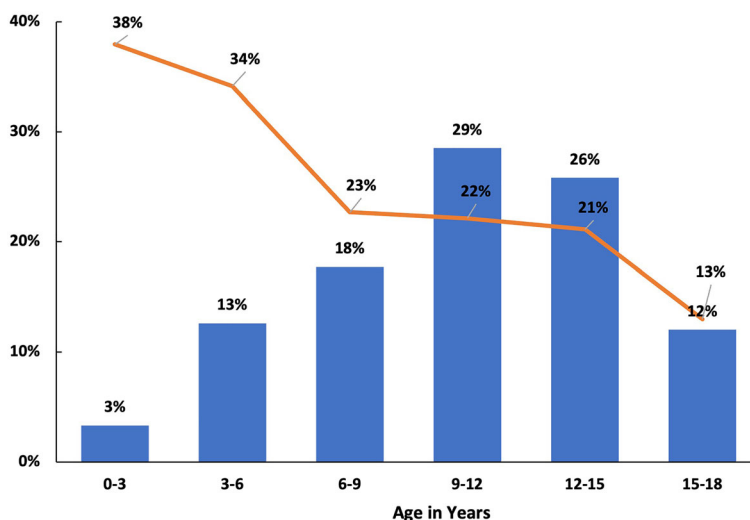


Fig. 1 Perforated appendicitis rates by age. The bar graph shows the study population segmented by age. The line graph represents perforation rate, by age, of all patients with appendicitis seen at St. Louis Children's Hospital from 2015–2019

5.6, $p = 0.02$). No significant differences in readmission rates were observed. In an attempt to account for variability in acuity, a comparison between patients discharged with only oral antibiotics ($N = 135$) versus patients discharged with no antibiotics ($N = 115$) was conducted. This analysis observed no difference in the rate of postoperative abscess formation (9% vs. 10%, $p = 0.79$), readmission rate (8% vs. 6%, $p = 0.39$), or average total LOS (5.7 vs. 5.6 days, $p = 0.13$).

The average admission WBC count among patients who developed postoperative abscess formation vs. those who did not was 17.5 vs. 17.0 ($p = 0.60$), respectively. Admission WBC count, regardless of age, was not correlated with subsequent LOS, antibiotic duration, postoperative abscess formation, or readmission, as outlined in Tables 5 and 6. There was, however, a significantly higher average discharge WBC count among patients who were subsequently readmitted versus those without readmission (11.4 vs. 9.9, $p < 0.01$). Additionally, patients discharged home with antibiotics had significantly higher average discharge WBC counts than those discharged without antibiotics (10.6 vs. 9.0, $p < 0.001$). Discharge WBC counts were not compared against postoperative abscess formation since the majority of abscesses developed while patients were still admitted.

A multivariable logistic regression analysis was conducted to determine the impact of exposures of interest on the formation of postoperative abscesses. Of note, initial broad-spectrum antibiotic use was associated with increased odds of postoperative abscess formation [OR = 3.17, 95% CI (1.58, 6.38)]. Odds of postoperative abscess formation were also significantly higher among male patients [OR = 2.18, (1.03, 4.60)], but were not significant for age, race, or admission WBC count.

DISCUSSION

Although the utility of intra-abdominal cultures in the setting of perforated appendicitis remains a subject for debate, our analysis shows that the yield of cultures diminishes as the collection moves further away from initial presentation, consistent with previous reports [17]. This is further illustrated by the seven cases where patients initially had bacterial growth on intraoperative culture only to later have a sterile culture at time of postoperative abscess formation. Although all cultures were pre-treated, since antibiotics are initiated prior to appendectomy or radiologic drainage, this trend is likely a product of ongoing antibiotic therapy. When bacterial growth was demonstrated, our

Table 2 Culture growth by culture type

	Pre-op drain	Intra-op	Post-op abscess	Blood
Total collected (% w/growth)	26 (96)	46 (87)	49 (51)	60 (5)
Total growth (% by culture type)				
<i>Bacteroides fragilis</i>	23 (88)	30 (65)	10 (20)	1 (2)
<i>Bacteroides vulgatus</i>	–	–	1 (2)	–
<i>Candida albicans</i>	–	1 (2)	1 (2)	–
<i>Clostridium</i> sp.	1 (4)	–	2 (4)	–
<i>Eggerthella lenta</i>	–	–	2 (4)	–
<i>Eikenella corrodens</i>	1 (4)	1 (2)	–	–
<i>Enterococcus faecalis</i>	1 (4)	–	2 (4)	–
<i>Enterococcus faecium</i>	–	–	3 (6)	–
<i>Enterococcus gallinarum</i>	–	–	1 (2)	–
<i>Escherichia coli</i>	19 (73)	32 (70)	10 (20)	2 (3)
<i>Fusobacterium</i> sp.	–	1 (2)	–	–
<i>Gemella</i> sp.	–	1 (2)	–	–
<i>Granulicatella</i> sp.	–	2 (4)	–	–
<i>Haemophilus influenzae</i>	–	1 (2)	–	–
<i>Klebsiella oxytoca</i>	–	–	1 (2)	–
<i>Klebsiella pneumoniae</i>	–	2 (4)	1 (2)	–
<i>Lactobacillus</i> sp.	–	–	1 (2)	–
Mixed aerobes	17 (65)	19 (41)	4 (8)	–
Mixed anaerobes	19 (73)	18 (39)	3 (6)	–
<i>Parvimonas</i> sp.	2 (8)	1 (2)	–	–
<i>Propionibacterium acnes</i>	–	–	1 (2)	–
<i>Pseudomonas aeruginosa</i>	1 (4)	7 (15)	6 (12)	–
<i>Slackia exigua</i>	1 (4)	–	–	–
<i>Streptococcus pyogenes</i>	–	1 (2)	–	–
Viridans group strep	17 (65)	21 (46)	10 (20)	–

findings were consistent with the literature, showing *B. fragilis*, *E. coli*, and Viridans group streptococcus as the most prevalent organisms [17, 18]. The rate of *P. aeruginosa* growth has been documented between 17 and 28% among intraoperative cultures [4, 17, 18]. However,

lower rates of *P. aeruginosa* were seen in our cohort: 15% of all intraoperative cultures and 12% of all postoperative abscess cultures. This difference may be due to geographic and environmental variability, but is also only an estimate of the true prevalence based on the sample

Table 3 Sequential surgical site culture summary

Summary of results for patients with both an intra- and postoperative abscess culture collection	
Patients with sequential cultures	11
Positive intraoperative cultures	11
Positive postoperative abscess cultures	4
Sterile postoperative abscess cultures	7
Identical growth on paired cultures	2

size of cultures obtained within the cohort. Tailoring antibiotic coverage based on intraoperative cultures may not have an impact on the development of post-surgical complications, although disagreement exists on the need to provide treatment for *P. aeruginosa* [18, 19]. In our cohort, the majority of patients did not receive cultures and had favorable clinical courses without pseudomonal coverage.

While the use of anti-pseudomonals, specifically, is beyond the scope of this article, our study is not the first to report the overall use of

Table 5 Correlation of average WBC with postoperative abscess formation and/or readmission

		<i>p</i> value
Average admission WBC		
Subsequent abscess (<i>n</i> = 49)	17.5	0.60
No abscess (<i>n</i> = 268)	17.0	
Average discharge WBC		
Subsequent readmission (<i>n</i> = 23)	11.4	< 0.01
No readmission (<i>n</i> = 309)	9.9	

broad-spectrum antibiotics is associated with worse clinical outcomes [6, 20]. Consideration should be given that patients presenting with a higher level of acuity are more likely to receive broader spectrum antibiotics, accounting for some of this association. In our study, clinical outcomes were considered based on the initial antibiotic regimen, which was decided prior to surgical intervention. While it could not be determined why specific antibiotic regimens were chosen, among patients who received

Table 4 Antibiotic regimen vs. outcomes of interest

	Initial antibiotic treatment		Discharge with antibiotics		Discharge antibiotics by route		
	Broad	Narrow	Yes	No	PO	IV	Mixed
Average LOS, days	7.0	5.7	6.4	5.6	5.7	8.5	9.7
<i>p</i> value	< 0.01		0.02	0.13			
Average antibiotic duration, days	13.5	10.4	13.1	6.3	11.9	16.1	18.7
<i>p</i> value	< 0.01		< 0.01	< 0.01			
Post-op abscesses (%)	25 (25)	27 (12)	38 (22)	14 (9)	13 (10)	15 (71)	10 (59)
<i>p</i> value	< 0.01		< 0.01	0.79			
Readmits (%)	8 (10)	15 (6)	14 (8)	9 (6)	11 (8)	1 (5)	2 (13)
<i>p</i> value	0.61		0.37	0.39			

Table 6 Correlation of admission WBC with key clinical outcomes

	Patients < 12 years		Patients > 12 years	
Median age	8.4		13.8	
Total				
WBC 0–15	64		46	
WBC 15+	133		74	
Average LOS				
WBC 0–15	5.9	$p = 0.27$	6.2	$p = 0.31$
WBC 15+	5.5		6.9	
Average antibiotic duration				
WBC 0–15	9.5	$p = 0.93$	11.2	$p = 0.32$
WBC 15+	9.6		12.5	
Post-op abscesses				
WBC 0–15	9 (14)	$p = 0.49$	7 (15)	$p = 0.16$
WBC 15+	14 (11)		19 (26)	
Readmissions				
WBC 0–15	4 (6%)	$p = 0.95$	2 (4%)	$p = 0.18$
WBC 15+	8 (6%)		8 (11%)	

broad-spectrum antibiotics there was a significantly higher rate of postoperative abscess formation, which could indicate a higher level of acuity. However, the length of stay, although significant, is only slightly longer than for patients who received metronidazole and a third-generation cephalosporin (7.0 vs. 5.7 days, $p < 0.01$). Additionally, the lack of significant difference in readmission rates between the two groups further suggests that initial management with metronidazole and a third-generation cephalosporin is appropriate and sufficient for most pediatric patients presenting with perforated appendicitis.

Previous studies have shown post-discharge antibiotics lack beneficial value, although this has only been considered in the setting of a normal WBC count at time of discharge [10–13]. Separately, it has also been shown that patients discharged with IV antibiotics experience equal

or greater rates of complications than those discharged with oral antibiotics [8, 9]. In our study, patients discharged with PO antibiotics had a statistically significant but clinically insignificant higher average WBC count than patients discharged without antibiotics (9.8 vs. 9.0, $p = 0.03$). In an attempt to account for illness severity, we compared LOS among these groups, an imperfect indicator for acuity, and found no significant difference. Additionally, the lack of difference in postoperative abscess formation and readmission rates supports the practice of discontinuing antibiotics at time of discharge for pediatric patients who are clinically well.

As aforementioned, WBC counts have historically been monitored throughout an admission for perforated appendicitis [10, 21]. In assessing admission WBC count versus other key metrics of interest, we found no significant correlation to suggest there is value in the ability to predict severity of illness. Conversely, discharge WBC counts have historically been an aide in determining whether or not to lengthen an admission or continue antibiotics at time of discharge [10, 11]. Although a previous study showed that postoperative abscesses are associated with higher rates of persistent leukocytosis 5–7 days postoperatively, no cases of abscess formation occurred among patients tolerating a regular diet 3 days postoperatively [14]. Our analysis showed a significant difference in discharge WBC count among patients who were later readmitted (11.4 vs. 9.9, $p < 0.01$), but this difference is not of clinical relevance and would not provide prospective value for the clinician. Thus, our study supports other findings that pediatric patients can be discharged safely when clinically well and without checking a final WBC count [15].

Limitations

This study is limited as a retrospective, single-center analysis and could be improved through subsequent prospective investigation. Similar investigations at multiple centers could help with generalizability, particularly in terms of the microbiology findings. During the period of

investigation (i.e., 2015–2019), the hospital underwent a transition in electronic medical records, which made certain facets of chart review difficult. Most significantly, a number of patients prior to this transition had documented discharge with antibiotics; however, no duration was listed, and prescribing information was unavailable. To prevent confounding, discharge antibiotics were primarily considered as a binary variable during data analysis, with patients either receiving a prescription or not. While total antibiotic course durations were reported, the actual difference would have been even greater had these data been available.

While the 5-year span of this study provides a robust cohort size, the temporal span may have confounding effects due to changes in antibiotic choices over time. Over the course of the study period, a significant decrease in the use of broad-spectrum antibiotic coverage occurred. Of the 73 patients initially treated with broad-spectrum antibiotics, 44 occurred in 2015, 12 occurred in 2016, and 5 to 6 per year occurred between 2017 and 2019. It is unlikely that this temporal aspect is significantly impacting the final results, since our conclusions generally show no significant difference between those who received broad-spectrum antibiotics and those who did not. It is also possible that initial broad-spectrum antibiotic use reflects illness severity, with sicker patients receiving broader coverage. However the year-over-year trend suggests that initial antibiotic choice may be impacted more by changing provider practice tendencies than by initial patient presentations.

As a single-site study, bacterial growth patterns may reflect geographical influences. The study also included a number of patients who were initially seen at an outside hospital ED and subsequently transferred for escalation of care after the diagnosis of appendicitis was made. In rare cases, it was not always possible to ascertain what interventions were provided at the outside hospital, namely antibiotic administration; however, patients were excluded if a significant portion of their care occurred at another hospital, so the impact on the included patients was likely minimal.

CONCLUSIONS

This study represents one of the largest and most recent epidemiologic evaluations of perforated appendicitis in children. Importantly, we identified common pathogens of perforated appendicitis, including *B. fragilis* and *E. coli*, and found that the yield of cultures diminishes over time in the postoperative period. While our analysis found a significant correlation between broad-spectrum antibiotics and postoperative abscesses, the routine use of broad-spectrum antibiotics, or continuing oral antibiotics beyond discharge, was not associated with improved clinically meaningful outcomes over using metronidazole and a third-generation cephalosporin alone until point of discharge. Finally, we found no association between trending WBC counts and clinical outcomes among pediatric patients with perforated appendicitis. Taken together, the findings in this study suggest that pediatric patients presenting with perforated appendicitis may be overtreated, in terms of antibiotic coverage and duration, and the monitoring of WBC counts, beyond the initial diagnosis, is not a reliable tool for this population.

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Author Contributions. Drs. Plattner, Shakhsher, and Newland conceptualized and designed the study. Dr. Plattner created the database, conducted data collection and initial analysis, and drafted the initial manuscript. Drs. Shakhsher and Newland supervised data

collection. Dr. Wallendorf carried out confirmatory data analysis. All authors critically reviewed the manuscript for important intellectual content.

Disclosures. Alex S. Plattner, Jason G. Newland, Michael J. Wallendorf, and Baddr A. Shakhsher declare that they have no conflict of interest.

Compliance with Ethics Guidelines. This study received approval from the Washington University in St. Louis institutional review board (IRB), ID #201908150.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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