Use of Antipseudomonal Antibiotics is Not Associated With Lower Rates of Postoperative Drainage Procedures or More Favorable Culture Profiles in Children With Complicated Appendicitis

Results From a Multicenter Regional Research Consortium

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Objective: To compare rates of postoperative drainage and culture profiles in children with complicated appendicitis treated with the 2 most common antibiotic regimens with and without antipseudomonal activity [piperacillin-tazobactam (PT) and ceftriaxone with metronidazole (CM)].

Background: Variation in the use of antipseudomonal antibiotics has been driven by a paucity of multicenter data reporting clinically relevant, culture-based outcomes.

Methods: A retrospective cohort study of patients with complicated appendicitis (7/2015–6/2020) using NSQIP-Pediatric data from 15 hospitals participating in a regional research consortium. Operative report details, antibiotic utilization, and culture data were obtained through supplemental chart review. Rates of 30-day postoperative drainage and organism-specific culture positivity were compared between groups using mixed-effects regression to adjust for clustering after propensity matching on measures of disease severity.

Results: In all, 1002 children met the criteria for matching (58.9% received CM and 41.1% received PT). In the matched sample of 778 patients, children treated with PT had similar rates of drainage overall [PT: 11.8%, CM: 12.1%; odds ratio (OR): 1.44 (OR: 0.71–2.94)] and higher rates of drainage associated with the growth of any organism [PT: 7.7%, CM: 4.6%; OR: 2.41 (95% CI: 1.08–5.39)] and *Escherichia coli* [PT: 4.6%, CM: 1.8%; OR: 3.42 (95% CI: 1.07–10.92)] compared to treatment with CM. Rates were similar between groups for drainage associated with multiple organisms [PT: 2.6%, CM: 1.5%; OR: 3.81 (95% CI: 0.96–15.08)] and *Pseudomonas* [PT: 1.0%, CM: 1.3%; OR: 3.42 (95% CI: 0.55–21.28)].

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Conclusions and Relevance: The use of antipseudomonal antibiotics is not associated with lower rates of postoperative drainage procedures or more favorable culture profiles in children with complicated appendicitis.

Keywords: antimicrobial stewardship, antipseudomonal antibiotics, complicated appendicitis, culture profiles, organ space infection, piperacillin-tazobactam

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Acute appendicitis is the most common abdominal surgical emergency in childhood and accounts for the greatest relative burden of surgical site infections among all pediatric surgical conditions.[1–3] Approximately 25% of children present with complicated disease, which is associated with relatively high rates of postoperative organ space infections (OSIs) requiring drainage procedures.[4,5] Appendicitis is also associated with the largest relative burden of antibiotic utilization among all pediatric surgical procedures, ranking third in the cumulative burden of antibiotic treatment days among all hospitalized children.[6,7] Efforts to balance antimicrobial stewardship with OSI prevention in children with complicated appendicitis therefore have important public health implications.

Whether the use of antipseudomonal antibiotics is necessary to optimize outcomes in children with complicated appendicitis remains controversial, and is reflected by the variation in the reported use of antipseudomonal agents in the literature.[5,8–10] Nearly 80% of children with complicated appendicitis are treated with either piperacillin-tazobactam (PT) or a combination of ceftriaxone and metronidazole (CM), which respectively represent the 2 most common antibiotic regimens with and without antipseudomonal activity.[5,11] Variation in antipseudomonal antibiotic use has likely been driven by limitations of existing comparative effectiveness data, including the lack of disease severity adjustment between groups, the use of heterogeneous definitions of exposures and outcomes, reliance on administrative data, the lack of generalizability due to small sample sizes, and conflicting data from existing multicenter studies.[5,8–10,12] Furthermore, there remains a paucity of multicenter data with culture-based outcomes to evaluate the in vivo efficacy of different antibiotic regimens.[13–15] Establishing whether the use of extended-spectrum, antipseudomonal antibiotics is associated with superior outcomes may have important implications for optimizing antimicrobial stewardship and infection prevention.[16–18]

With the considerations above, the goal of this analysis was to compare rates of postoperative drainage procedures and microbiological culture profiles between children treated with PT or CM at 15 children's hospitals, collectively representing a wide range of patient populations and geographic locations. Postoperative drainage was chosen as the primary outcome to represent clinically significant OSI events where the potential morbidity of a drainage procedure was considered justified based on imaging findings and clinical status. Furthermore, the utilization of drainage procedures as the primary outcome allowed for the comparative assessment of culture data between antibiotic treatment groups.

METHODS

Study Design and Data Source

This was a multicenter cohort study including patients from hospitals participating in the Eastern Pediatric Surgery Network (EPSN) regional research consortium. Data from the American College of Surgeons National Surgical Quality Improvement Program-Pediatric (NSQIP-Pediatric) Appendectomy Procedure Targeted Variables were obtained and augmented with supplemental chart review at each participating center. The NSQIP-Pediatric database includes appendicitis-focused clinical and outcomes data that are used for comparative performance and resource utilization reporting among its 160 member hospitals.[19] NSQIP-Pediatric data are collected by dedicated surgical clinical reviewers at each site using standardized definitions and chart review methods. Integrity and consistency of NSQIP-Pediatric data is facilitated through periodic site auditing, mandatory recertification of clinical reviewers, and the availability of American College of Surgeons clinical support to address questions regarding data abstraction protocols.[19,20]

All study sites performed supplemental chart reviews to collect operative reports, antibiotic utilization, and culture data from drainage procedures for patients identified from NSQIP-Pediatric data. One of the study sites did not participate in NSQIP-Pediatric and employed an alternative chart abstraction method replicating the NSQIP-Pediatric data collection process. Each site was required to review a manual of operations and training videos for data abstraction before beginning data collection. Mandatory data audits were required at each site after the collection of the first 10 cases to assess the accuracy and address any data collection questions. Study data were uploaded directly to the data coordinating center using a secure transfer process. The American College of Surgeons was not involved in the management or transfer of study data.

To explore the influence of antipseudomonal antibiotics on outcomes, analyses were performed at both the patient-level and hospital-level, as complementary approaches. A hospital-level analysis was performed to explore the correlation between hospitals' rates of antipseudomonal antibiotic utilization and rates of drainage procedures after adjusting for differences in disease severity among hospitals. A propensity-matched patient-level analysis was performed to explore whether children receiving antipseudomonal antibiotics had better outcomes compared to those that did not while adjusting for differences in disease severity at the level of individual patients.

This study was approved by the institutional review board of Boston Children's Hospital (IRB-00040592), which served as the study's coordinating center for the EPSN.

Study Cohort

Children aged 3 to 18 years undergoing appendectomy for complicated appendicitis were identified from the NSQIP-Pediatric database from July 1, 2015, to June 30, 2020, at each of the 16 EPSN hospitals. Complicated appendicitis was defined as the presence of one of the previously validated NSQIP-Pediatric intraoperative criteria of complicated disease in the dictated operative report [visible hole, extraluminal fecalith, abscess, or diffuse fibrinopurulent exudate (DFE) outside of the right lower quadrant and pelvis].[4,21] High-severity disease was defined as the presence of more than 1 NSQIP-Pediatric intraoperative criteria for complicated appendicitis, which has been shown to be associated with increased rates of adverse outcomes and resource utilization compared to the presence of only one finding.[21]

Children with complicated appendicitis were considered for inclusion in both the patient-level and hospital-level analysis if they received care at a hospital whose preferred regimen for complicated appendicitis was either PT or CM (15 of the 16 EPSN hospitals). Exclusion criteria included the use of antibiotics without colorectal coverage, administration of fewer than

2 days of inpatient antibiotics, or missing antibiotic data. Patients who did not receive either PT or CM preoperatively, received both preoperatively, or were simultaneously treated with a broader agent (eg, meropenem) were excluded from the patient-level analysis (Fig. 1).

Definition of Antibiotic Treatment Groups and Outcomes

Antibiotic treatment groups (PT or CM) for the patient-level analysis were assigned based on the antibiotic regimen received preoperatively to mimic an intent-to-treat approach based on empiric antibiotic choice. This approach was taken to minimize potential confounding by indication in the comparative analysis for children whose antibiotics may have been changed based on intraoperative findings or postoperative clinical course.

The primary study outcomes included rates of 30-day postoperative drainage procedures for OSIs. Postoperative drainage procedures were identified using NSQIP-Pediatric Procedure Targeted Appendectomy data and confirmed through supplemental chart review.[19] Secondary outcomes included rates of OSI with or without drainage, culture positivity with any organism, multiple organisms, *Escherichia coli*, and Pseudomonas species.

Statistical Analysis

χ^2 and Wilcoxon rank sum tests were used for univariate comparisons. The hospital-level analysis explored the correlation between postoperative PT utilization rates (as a surrogate for the intensity of antipseudomonal treatment at each hospital) and observed-to-expected (O/E) ratios of postoperative drainage procedures after adjusting for differences in disease severity profiles (based on the number and distribution of NSQIP-Pediatric intraoperative criteria for complicated disease) among hospitals. Hospital's O/E ratios were estimated by exponentiating the shrinkage estimate of each hospital's random effect from a mixed-effects logistic regression model.[22] The strength of the correlation was evaluated using a Spearman correlation test.

For the patient-level analysis, propensity score matching was used to balance measures of disease severity across the preoperative antibiotic treatment groups. A logistic regression model was used to calculate propensity scores for each patient, adjusting for the number (one vs multiple) and distribution of previously validated intraoperative NSQIP-defined findings of complicated appendicitis.[4,21] After propensity scores were calculated, children were matched 1:1 across PT and CM groups using a greedy matching algorithm. Mixed-effects logistic regression was used in the matched cohorts to estimate the association between antibiotic treatment groups and outcomes, adjusting for hospital-level event clustering. Measures of association were reported as adjusted odds ratios (ORs).

Analyses were performed with SAS statistical software (version 9.4; SAS Institute, Inc.). The threshold for statistical significance was defined as a two-sided $P < 0.05$.

RESULTS

After applying exclusion criteria, 1268 children with complicated appendicitis from 15 EPSN hospitals were included in the hospital-level analysis (median: 84 patients/hospital). Of these, 79.0% (1002) received either PT (41.1%) or CM (58.9%) preoperatively and were available for propensity score matching, with 778 matched into PT and CM treatment groups for the patient-level analysis (Fig. 1).

Before matching, children treated with PT preoperatively had higher severity disease compared to those treated with CM (Table 1). Following matching, no differences in disease severity remained, and matched groups were also similar in demographic characteristics, case duration, and postoperative length of stay (Table 1).

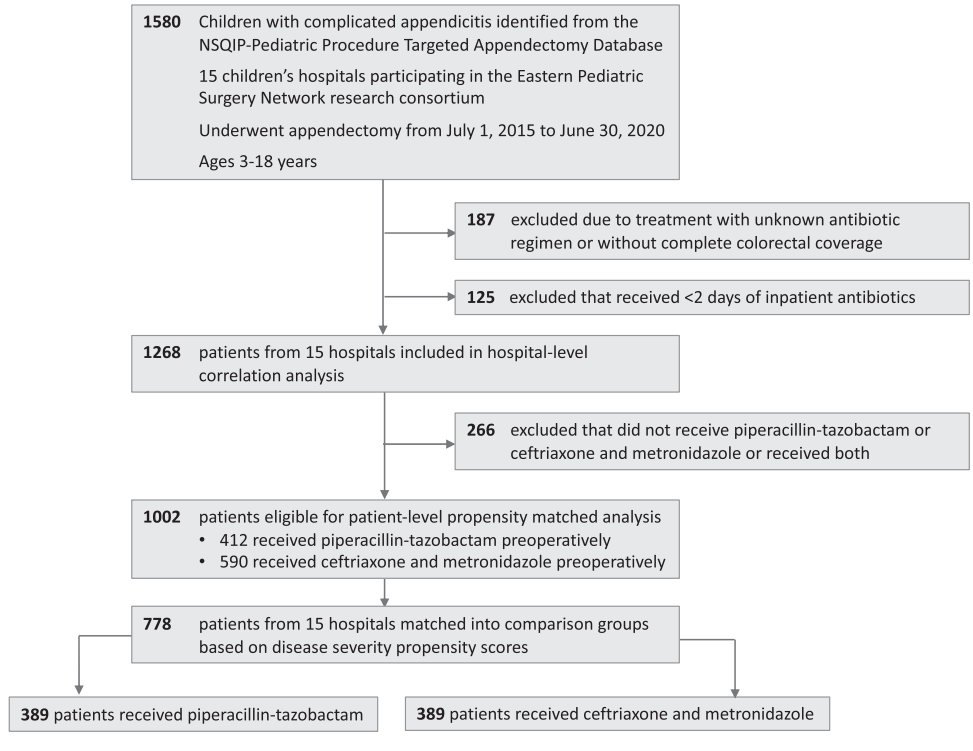

FIGURE 1. Assembly of the study cohorts for the hospital and patient-level analyses.

TABLE 1. Demographic Characteristics and Measures of Appendicitis Severity in Children With Complicated Appendicitis Treated With Piperacillin-Tazobactam and Ceftriaxone With Metronidazole Before and After Propensity Matching

	Entire cohort			Propensity-matched* cohort		
	Piperacillin-tazobactam	Ceftriaxone and metronidazole	*P*	Piperacillin-tazobactam	Ceftriaxone and metronidazole	*P*
Patient demographics	(N = 412)	(N = 590)		(N = 389)	(N = 389)	
Age at operation, median (IQR)	9 (7–12)	10 (7–12)	0.42	9 (7–12)	10 (7–12)	0.44
Female sex, N (%)	155 (37.6)	233 (39.5)	0.55	149 (38.3)	150 (38.6)	0.94
Measures of appendicitis severity						
Postoperative length of stay, median (IQR)	4 (3–6)	4 (3–6)	0.26	4 (3–6)	4 (3–6)	0.66
Operative duration in minutes, median (IQR)	60 (46–78)	58 (44–75)	0.12	60 (46–78)	58 (44–79)	0.49
Multiple intraoperative findings of complicated disease, N (%)*	249 (60.4)	284 (48.1)	< 0.01	226 (58.1)	229 (58.9)	0.83
Visible hole, N (%)*	358 (86.9)	503 (85.3)	0.46	335 (86.1)	341 (87.7)	0.52
Extraluminal fecalith, N (%)*	85 (20.6)	92 (15.6)	0.04	76 (19.5)	76 (19.5)	1.00
Abscess, N (%)*	168 (40.8)	173 (29.3)	< 0.01	145 (37.3)	139 (35.7)	0.66
Diffuse fibrinopurulent exudate, N (%)*	142 (34.5)	169 (28.6)	0.05	119 (30.6)	122 (31.4)	0.82

*Matched on number and relative distribution of National Surgical Quality Improvement Program-Pediatric criteria for complicated appendicitis.
IQR indicates interquartile range.

Antibiotic Utilization Trends

Of the 1268 patients included in the hospital-level analysis, the most common postoperative antibiotic regimens were CM (50.0%; hospital range: 0%–96.0%), PT (40.4%, hospital range: 0%–99.5%), ampicillin-sulbactam (3.3%; hospital range: 0%–39.8%), ertapenem (2.7%; hospital range: 0%–23.7%), and ciprofloxacin with metronidazole (1.9%; hospital range: 0%–9.7%; Fig. 2). Overall, PT represented 95.4% of all regimens with antipseudomonal activity, and CM represented 87.0% of all regimens without antipseudomonal activity.

In the matched cohort for the patient-level analysis, the most common postoperative antibiotics used in the 389 children treated with PT preoperatively included PT (95.4%), CM (2.8%), and PT with metronidazole (0.5%). In the 389 matched children treated with CM preoperatively, the most used postoperative antibiotics included CM (93.3%), PT (4.1%), and ciprofloxacin with metronidazole (1.3%). Antibiotic regimens remained unchanged in the postoperative period in 94.3% of patients, which did not differ between treatment groups (PT: 95.4% vs CM: 93.3%, $P = 0.21$).

Postoperative OSIs and Drainage Procedures

In the hospital-level analysis, the overall postoperative drainage rate was 10.8% (137/1268) and ranged from 0% to 25.8% among hospitals (Fig. 2). No correlation was found between hospital-level rates of PT utilization and postoperative drainage (Spearman ρ: 0.21, $P = 0.46$; Fig. 2), nor between rates of PT utilization and O/E ratios of drainage rates after adjustment for differences in disease severity among hospitals (Spearman ρ: 0.02, $P = 0.94$).

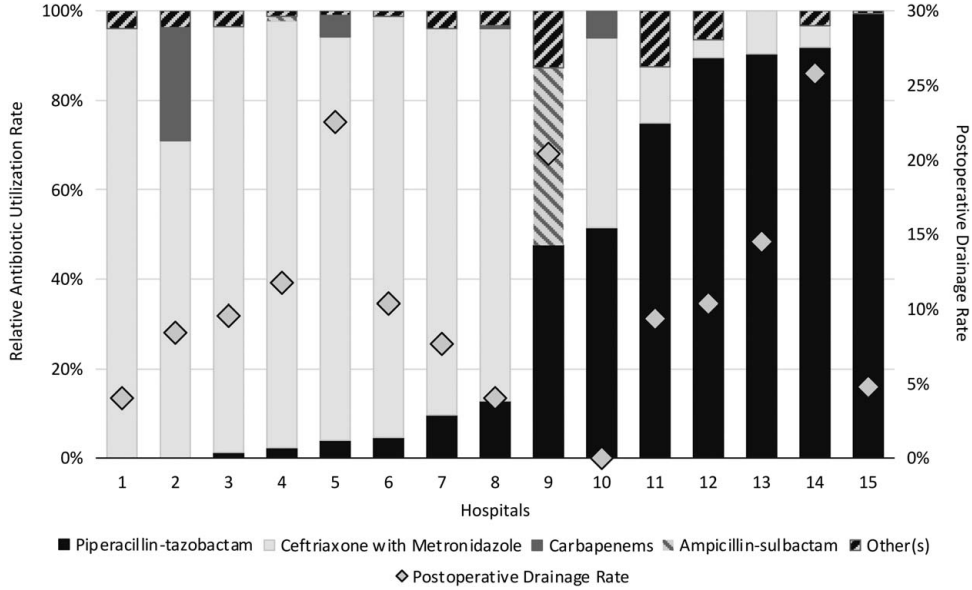

FIGURE 2. Variation in preferred antibiotic regimens (based on antibiotics used on postoperative day 1) and postoperative drainage procedures in all children with complicated appendicitis at 15 hospitals participating in a regional research consortium.

Drainage and Culture Outcomes	Unadjusted Rates, N (%) PT (N=389)	CM (N=389)	Adjusted OR (95% CI)
Postoperative drainage procedure	46 (11.8%)	47 (12.1%)	1.44 (0.71-2.94)
with any organism growth	30 (7.7%)	18 (4.6%)	2.41 (1.08-5.39)
with growth of multiple organisms	10 (2.6%)	6 (1.5%)	3.81 (0.96-15.08)
with Escherichia coli growth	18 (4.6%)	7 (1.8%)	3.42 (1.07-10.92)
with Pseudomonas growth	4 (1.0%)	5 (1.3%)	3.42 (0.55-21.28)
with any other organism growth	17 (4.4%)	12 (3.1%)	1.96 (0.77-5.00)

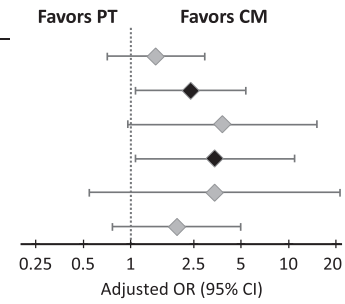

FIGURE 3. Association between the antibiotic treatment group and postoperative drainage outcomes in children with complicated appendicitis treated with piperacillin-tazobactam (PT) or ceftriaxone with metronidazole (CM). Unadjusted rates are reported along with adjusted odds ratios (OR) and 95% CIs. The magnitude and direction of outcome differences between adjusted and unadjusted data (notably for overall drainage and drainage associated with *Pseudomonas* growth) were driven by hospital-level clustering of events.

In the patient-level analysis, the overall postoperative drainage rate was 11.1% (111/1002) and rates were similar between treatment groups (PT: 11.7% vs CM: 10.7%, $P = 0.63$). In the cohort of 778 children propensity matched based on disease severity, rates of OSI requiring drainage remained similar between treatment groups (PT: 11.8% vs CM: 12.0%, $P = 0.31$; Fig. 3). The rate of any OSI (with or without drainage) was similar in children treated with PT when compared to CM in the overall cohort before matching (PT: 17.0% vs CM: 13.1%, $P = 0.08$) and in the propensity-matched cohort (PT: 16.2% vs CM: 14.7%, $P = 0.55$).

Postoperative Culture Data

Of the 111 children receiving either PT or CM who underwent drainage procedures, 104 (93.7%) from 14 different hospitals had aspirates sent for culture (PT: 48, CM: 56). Cultures were positive in 52.9% of aspirates and 19.2% grew more than one organism. The most frequently isolated organisms were *E. coli* (26.9%), *Streptococcus* species (14.4%), and *Pseudomonas* species (10.5%) (Fig. 4). Compared to aspirates from children treated with CM, aspirates from children treated with PT were more likely to grow *E. coli.* and had similar rates of growth of *Pseudomonas* species (Fig. 4). Rates of culture growth of any organism and multiple organisms were also similar between treatment groups.

In the propensity-matched sample, children treated with PT had higher rates of drainage procedures associated with the growth of any organism and *E. coli.* compared to those treated with CM, and similar rates of drainage procedures associated with the growth of multiple organisms and *Pseudomonas* species compared to children treated with CM (Fig. 3).

DISCUSSION

In this multicenter analysis of 1002 children from 15 hospitals, the use of PT was not associated with lower rates of postoperative drainage or more favorable microbiological culture profiles compared to treatment with CM. Furthermore, increasing rates of PT utilization were not correlated with lower rates of postoperative drainage at the hospital level. These complementary analyses provide compelling evidence that empiric use of antipseudomonal antibiotics is not necessary to optimize outcomes in children with complicated appendicitis.

The results of this analysis provide important new insight into the relatively limited pool of multicenter comparative data exploring antibiotic-associated outcomes in children with

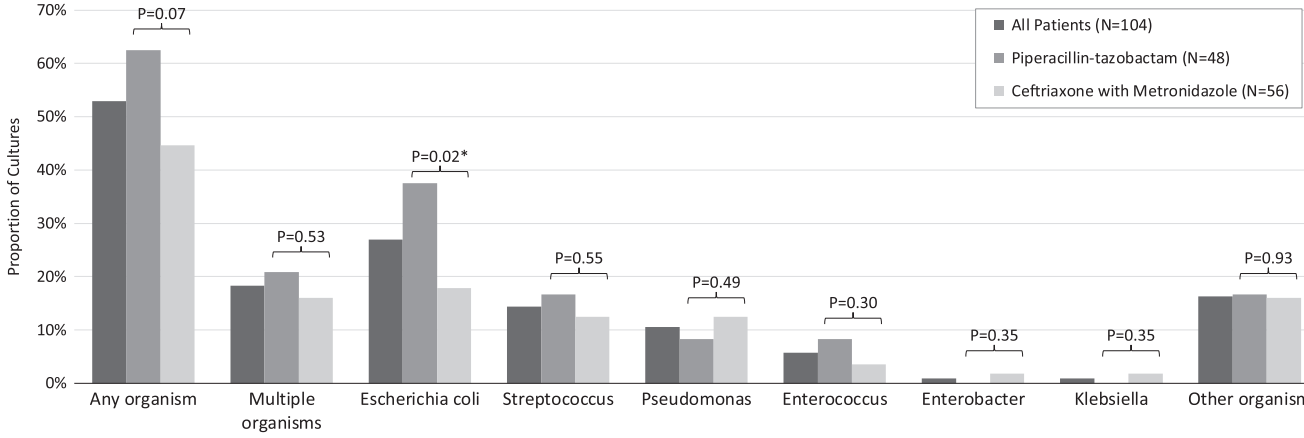

FIGURE 4. Culture results from 104 children with complicated appendicitis undergoing postoperative drainage procedures from 14 different hospitals (*P* values correspond to comparison between antibiotic treatment groups and * denotes a significant result with $P < 0.05$).

complicated appendicitis. In a retrospective analysis of 29,015 children using the Pediatric Health Information System database, treatment with PT was associated with higher rates of postoperative drainage compared to CM although outcomes were equivalent after adjustment for differences in practice patterns.[23] This analysis was limited in its reliance on administrative data for defining both exposures and outcomes, as well as the inability to adjust for differences in disease severity. This latter limitation has important implications for the interpretation of the data given in the present study patients receiving PT had more severe disease compared to those receiving CM before severity adjustment. In another retrospective multicenter analysis of 654 patients from 14 NSQIP-Pediatric hospitals, patients treated with PT had similar rates of postoperative OSI compared to those receiving CM after adjusting for disease severity.[5] The validity of this analysis benefited from the use of validated severity-adjustment methods and the use of NSQIP-Pediatric data for outcomes assessment but was limited in its use of administrative data for defining antibiotic exposure groups. In contrast, a randomized trial including 162 children with complicated appendicitis from 2 hospitals reported a nearly 4-fold higher OSI rate associated with CM use compared to PT.[12] The external generalizability of these findings may be limited; however, as the benefit of PT was primarily driven by one of two hospitals participating in the trial. The other hospital did not change its practice, continuing to use CM as first-line treatment for complicated appendicitis despite the results of the published analysis (A. Wirtz, PharmD; Co-Director, Antimicrobial Stewardship Program, Children's Mercy Kansas City; personal written communication, June 9, 2023). As with all previous multicenter studies, the results of this trial were limited by a lack of culture data from drainage procedures.

The present analysis has several notable strengths when compared to previously published studies. Whereas prior multicenter studies were limited to the use of administrative data, the data for the present analysis were obtained through standardized chart review by NSQIP-Pediatric and EPSN study personnel. Propensity score matching was used to balance disease severity between treatment groups in the patient-level analysis based on validated measures of disease severity that have been shown to influence OSI risk in children with complicated appendicitis.[4,21] Postoperative drainage was chosen as the primary outcome to represent clinically relevant OSIs consequential enough to justify the potential morbidity of a drainage procedure and anesthesia. The inclusion of a hospital-level analysis using severity-adjusted outcomes provides additional insight into the relative effectiveness of antipseudomonal agents by comparing outcomes at hospitals over the extreme range of utilization. In this regard, it is noteworthy that hospitals that nearly exclusively used one regimen or the other had a similar distribution of postoperative drainage rates. Finally, this study includes the largest and first multicenter analysis of drainage-associated culture data in children with complicated appendicitis, providing relevant supplemental information for the in vivo assessment of different antibiotic regimens. Based on these considerations, we believe this analysis provides the most robust and generalizable results to date in characterizing the comparative effectiveness of extended-spectrum antipseudomonal antibiotic use in children with complicated appendicitis.

There were several findings from the analysis of culture data that deserve mention. Rates of overall *Pseudomonas* growth and drainage procedures with *Pseudomonas* positivity were similar between patients treated with PT and CM, as were rates of growth of multiple organisms. Interestingly, children treated with PT had higher rates of drainage procedures associated with any culture positivity and *E. coli* growth compared to those treated with CM. These data suggest that the extended spectrum of in vitro activity associated with PT (relative to CM) may not translate into reduced growth of *Pseudomonas* species or other organisms from abscess cultures in children with complicated appendicitis. Furthermore, the use of PT may be less efficacious at inhibiting the growth of *E. coli*, a common organism isolated from both intraoperative and peritoneal cultures in children with complicated appendicitis.[13,14,24,25] These findings are particularly notable when considering the existing evidence that postoperative culture results are poorly predicted by intraoperative culture data.[13,15] Further investigation is warranted to explore these observations to better understand the apparent differences between in vitro and in vivo antimicrobial efficacy in this cohort of children.

The results of this study must be interpreted within the context of its limitations. Data were retrospectively collected and errors in misclassification were possible despite rigorous, standardized chart review methods. Confounding by indication, where children with more severe disease may be treated with broader spectrum antibiotics, was also a possibility given the retrospective study design. Several approaches were used to mitigate this potential bias, including a preoperative intention-to-treat approach for assigning treatment groups, the use of propensity matching in the patient-level analysis to balance treatment groups on validated measures of disease severity, and the use of a complementary, severity-adjusted hospital-level analysis. It is also noteworthy that 95% of patients had the same antibiotics continued postoperatively as they received preoperatively, and rates were similar between patients receiving PT or CM. This observation strongly suggests that antibiotic choice was primarily driven by surgeon or hospital preference. Despite a relatively large sample size, drainage procedures associated with specific organisms were uncommon, and therefore some analyses were likely underpowered to detect differences in organism-specific culture positivity between treatment groups. However, the small absolute differences observed in culture outcomes among treatment groups (eg, 0.3% absolute difference between groups in drainage rates associated with *Pseudomonas* growth) suggest any differences between groups are likely to carry little clinical significance. Finally, hospitals participating in the EPSN research consortium are largely academic children's hospitals, which may limit the generalizability of these data to other clinical settings.

Despite the above limitations, these data support abandoning the empiric use of PT in favor of the more narrow-spectrum regimen of CM. This practice change could have important implications for antimicrobial stewardship in surgery as inappropriate utilization of antibiotics has been identified as a key modifiable driver of antimicrobial resistance.[18] Antipseudomonal antibiotics in particular have been identified as a high priority target for stewardship and drug development efforts.[16,17] When considering the existing variation in practices and the burden of treatment days associated with appendicitis, limiting the empiric use of antipseudomonal antibiotics in children with complicated appendicitis could have a meaningful impact on antimicrobial stewardship in pediatric surgery.[6,7]

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