

Postoperative Antibiotics, Outcomes, and Resource Use in Children With Gangrenous Appendicitis

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IMPORTANCE Gangrenous, suppurative, and exudative (GSE) findings have been associated with increased surgical site infection (SSI) risk and resource use in children with nonperforated appendicitis. Establishing the role for postoperative antibiotics may have important implications for infection prevention and antimicrobial stewardship.

OBJECTIVE To compare SSI rates in children with nonperforated appendicitis with GSE findings who did and did not receive postoperative antibiotics.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study using American College of Surgeons' National Surgical Quality Improvement Program (NSQIP)-Pediatric Appendectomy Targeted data from 16 hospitals participating in a regional research consortium. NSQIP data were augmented with operative report and antibiotic use data obtained through supplemental medical record review. Children with nonperforated appendicitis with GSE findings who underwent appendectomy between July 1, 2015, and June 30, 2020, were identified using previously validated intraoperative criteria. Data were analyzed from October 2022 to July 2023.

EXPOSURE Continuation of antibiotics after appendectomy.

MAIN OUTCOMES AND MEASURES Rate of 30-day postoperative SSI including both incisional and organ space infections. Complementary hospital and patient-level analyses were conducted to explore the association between postoperative antibiotic use and severity-adjusted outcomes. The hospital-level analysis explored the correlation between postoperative antibiotic use and observed to expected (O/E) SSI rate ratios after adjusting for differences in disease severity (presence of gangrene and postoperative length of stay) among hospital populations. In the patient-level analysis, propensity score matching was used to balance groups on disease severity, and outcomes were compared using mixed-effects logistic regression to adjust for hospital-level clustering.

RESULTS A total of 958 children (mean [SD] age, 10.7 [3.7] years; 567 male [59.2%]) were included in the hospital-level analysis, of which 573 (59.8%) received postoperative antibiotics. No correlation was found between hospital-level SSI O/E ratios and postoperative antibiotic use when analyzed by either overall rate of use (hospital median, 53.6%; range, 31.6%-100%; Spearman $\rho = -0.10$; $P = .71$) or by postoperative antibiotic duration (hospital median, 1 day; range, 0-7 days; Spearman $\rho = -0.07$; $P = .79$). In the propensity-matched patient-level analysis including 404 patients, children who received postoperative antibiotics had similar rates of SSI compared with children who did not receive postoperative antibiotics (3 of 202 [1.5%] vs 4 of 202 [2.0%]; odds ratio, 0.75; 95% CI, 0.16-3.39; $P = .70$).

CONCLUSIONS AND RELEVANCE Use of postoperative antibiotics did not improve outcomes in children with nonperforated appendicitis with gangrenous, suppurative, or exudative findings.

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Appendicitis is the most common abdominal surgical emergency in children, accounting for the greatest relative burden of surgical site infections (SSIs) in pediatric surgery.¹⁻³ Management of appendicitis is also associated with substantial antibiotic use, ranking third in cumulative number of antibiotic treatment days in hospitalized children behind only pneumonia and cystic fibrosis.^{4,5} When considering the public health implications of SSIs and antimicrobial resistance, optimizing SSI prevention while minimizing antibiotic overuse should be considered a high priority goal within pediatric surgery.⁶⁻⁸

Whether continuation of antibiotics postoperatively is beneficial in children with nonperforated appendicitis associated with gangrenous, suppurative, or exudative (GSE) findings remains a controversial topic. In a multicenter study including 6133 children with nonperforated appendicitis, the presence of GSE findings was associated with increased length of stay and higher rates of SSI and hospital revisits compared with cases where GSE findings were absent.⁹ Whether this increase in SSI rates and resource use can be mitigated by postoperative continuation of antibiotics remains uncertain, with available data limited to small, single-center experiences using heterogeneous definitions for both exposures and outcomes.¹⁰⁻¹²

With these considerations, the goal of this analysis was to evaluate whether use of postoperative antibiotics was associated with improved outcomes in children with nonperforated appendicitis with GSE findings from 16 children's hospitals, collectively representing a wide range of patient populations and practice environments. Establishing the benefit, if any, of postoperative antibiotics in children with GSE findings would potentially have important implications for optimizing SSI prevention or antimicrobial stewardship, depending on the relative comparative effectiveness associated with extended treatment.

Methods

Study Design and Data Source

This cohort study was approved by the institutional review board of the data coordinating center, Boston Children's Hospital. The Boston Children's Hospital institutional review board deemed this retrospective cohort study to be minimal risk and exempt as human subjects research, therefore informed consent was not required. This was a multicenter study including 16 hospitals participating in the Eastern Pediatric Surgery Network (EPSN) regional research consortium. Data from the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP)-Pediatric Appendectomy Procedure Targeted Variables were obtained and augmented with supplemental medical record review at each participating center. The NSQIP-Pediatric database includes appendicitis-specific clinical data used to compare risk-adjusted adverse event and resource use data among its 160 member hospitals.¹³ NSQIP-Pediatric data are collected by dedicated surgical clinical reviewers using standardized definitions and medical record review methods. Accuracy of these data is ensured by periodic auditing, mandatory recertification

Key Points

Question In children with nonperforated appendicitis with gangrenous, suppurative, or exudative findings, is continuation of postoperative antibiotics associated with a reduction in surgical site infection risk and resource use?

Findings In this multicenter cohort study of 958 children from 16 hospitals using complementary hospital and patient-level analyses, no association was found between postoperative antibiotic use and postoperative risk of surgical site infection, abdominal imaging, or hospital revisits.

Meaning Use of postoperative antibiotics did not improve outcomes in children with nonperforated appendicitis with gangrenous, suppurative, or exudative findings.

of reviewers, and the availability of American College of Surgeons clinical support to address questions regarding data abstraction protocols.^{13,14} This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

All study sites performed supplemental medical record review to collect antibiotic use and operative report data for patients identified in the NSQIP-Pediatric database. One of the study sites did not participate in NSQIP-Pediatric and used an alternative medical record 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 collection of the first 10 cases to assess 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 association of postoperative antibiotics with outcomes, both patient and hospital-level analyses were performed to provide complementary approaches. The goal of the patient-level analysis was to explore whether children with nonperforated appendicitis with GSE findings who received postoperative antibiotics had better outcomes compared with those who did not, after adjustment for differences in disease severity between treatment groups. The goal of the hospital-level analysis was to explore whether children treated at hospitals with greater postoperative antibiotic use had better outcomes than those treated at hospitals with less antibiotic use, after adjustment for differences in severity profiles among hospital populations.

Study Cohort

Children aged 3 to 17 years who underwent appendectomy for nonperforated appendicitis from July 1, 2015, to June 30, 2020, at the 16 participating consortium hospitals were identified from NSQIP-Pediatric data. Nonperforated appendicitis was defined as the absence of the 4 previously validated NSQIP-Pediatric intraoperative criteria of complicated appendicitis: visible hole, extraluminal fecalith, abscess, or diffuse fibrinopurulent exudate outside of the right lower quadrant

and pelvis.^{8,15} Cases of nonperforated appendicitis with GSE findings directly involving the appendix were considered for inclusion. The presence of GSE findings was established through a standardized, keyword-based review of operative report text for each case, which has previously been validated and shown to have high interrater reliability.⁹ Children with missing data for exposures or outcomes were excluded. Race and ethnicity were not reported as part of this analysis because these data were not reliably reported in NSQIP-Pediatric (41% of the cohort was categorized as unknown) and are unlikely to be important predictors of a patient's response to antibiotics.

Classification of Exposure and Outcomes

The primary exposure was empirical use of any postoperative antibiotics during the index hospitalization or prescribed at discharge. Postoperative antibiotic duration was defined as the combined number of postoperative antibiotic treatment days received during the index hospitalization and prescribed at discharge. Study outcomes included 30-day rates of postoperative SSI (incisional and organ space as defined by NSQIP-Pediatric), postoperative abdominal imaging (ultrasonography, computed tomography, or magnetic resonance imaging), and hospital revisits (including emergency department visits and inpatient readmissions).

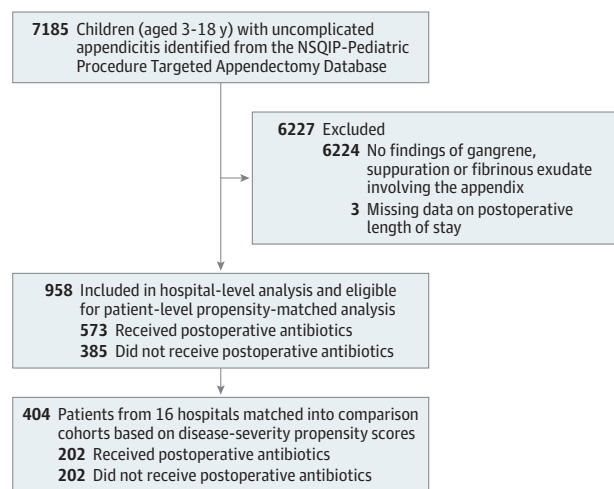
Statistical Analysis

For univariate comparisons, χ^2 and Wilcoxon rank sum tests were used. The hospital-level analysis explored the correlation between hospitals' postoperative antibiotic use and outcomes. Separate correlations were calculated for 2 measures of hospitals' use of postoperative antibiotics: rate of use and mean duration of postoperative antibiotic use. Spearman correlations were used to compare these measures of antibiotic use with hospitals' 30-day postoperative rates of SSI, imaging use, and revisit. Outcomes were adjusted using observed to expected (O/E) ratios to adjust for hospitals' individual cohorts mean age, rate of gangrene, and mean postoperative length of stay (PLOS). Hospital-level O/E ratios were estimated by exponentiating the shrinkage estimate of each hospital's random effect from a mixed-effects regression model.¹⁶

For the patient-level analysis, propensity score matching was used to balance the comparison groups. A logistic regression model was used to calculate propensity scores for each patient, using patient age at appendectomy, high severity intraoperative disease (defined as presence of gangrene), and clinical severity (for which PLOS served as a proxy) as covariates.⁹ After propensity scores were calculated, children were matched 1:1 across groups using a greedy matching algorithm. Mixed-effects logistic regression was then used in the matched cohorts to estimate the association between use of any postoperative antibiotics and outcomes, adjusting for hospital-level clustering. Measures of association were reported as adjusted odds ratios (ORs).

Analyses were performed with SAS statistical software, version 9.4 (SAS Institute). The threshold for statistical significance defined as a 2-sided $P < .05$. Data were analyzed from October 2022 to July 2023.

Figure 1. Study Cohort



Assembly of the hospital-level and propensity matched study cohorts.
NSQIP indicates National Surgical Quality Improvement Program.

Results

In total, 7185 children with nonperforated appendicitis were identified, of which 961 (13.4%) had GSE findings documented in the operative report. After applying exclusion criteria, 958 children (mean [SD] age, 10.7 [3.7] years; 567 male [59.2%]; 391 female [40.8%]) with GSE findings were included in the hospital-level analysis and were available for propensity matching, of which 573 (59.8%) received postoperative antibiotics (Figure 1).

Prior to matching and compared with children who did not receive postoperative antibiotics, children who received antibiotics postoperatively were more likely to have higher severity disease based on the presence of gangrene (347 of 573 [60.6%] vs 115 of 385 [29.9%], longer PLOS (≥ 3 days, 149 of 573 [26.0%] vs 1 of 385 [0.3%]), and longer operative duration (median [IQR], 46 [35-64] minutes vs 41 [32-53] minutes) (Table). After matching based on age, presence of gangrene, and PLOS, children who did not receive postoperative antibiotics were similar to those who did in measures of disease severity, including presence of gangrene (72 of 202 [35.6%] vs 72 of 202 [35.6%]), PLOS (≥ 3 days, 1 of 202 [0.5%] vs 1 of 202 [0.5%]), operative duration (median [IQR], 45 [36-59] minutes vs 44 [35-54] minutes), and age (mean [SD], 10.9 [3.8] years vs 11.1 [3.7] years).

Postoperative Antibiotic Use

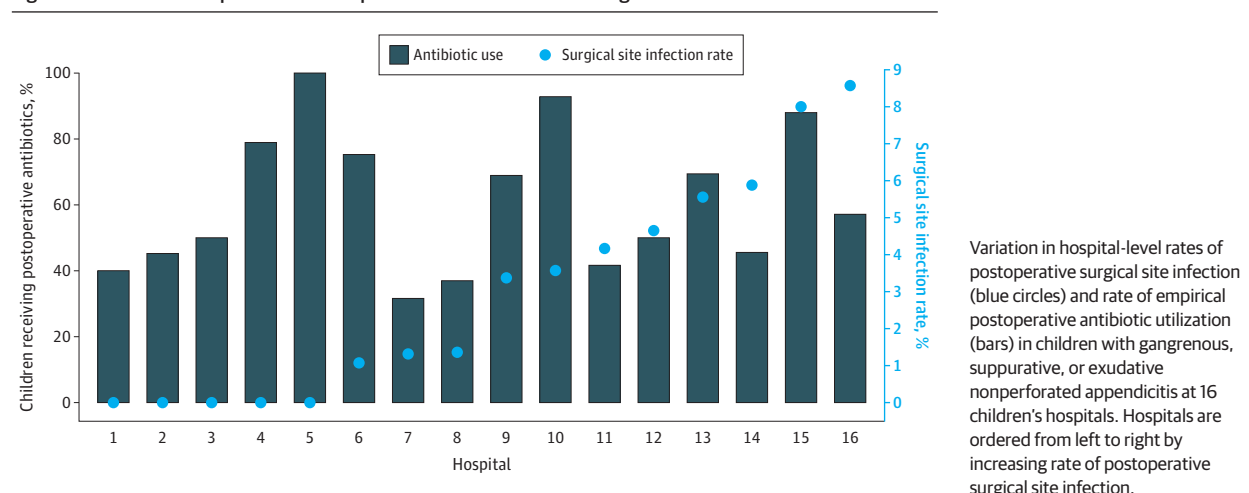
Of the 958 children included in the hospital-level analysis, 573 (59.8%) received postoperative antibiotics (hospital median, 53.6%; range, 31.6%-100%; $P < .001$) (Figure 2), and 319 (33.3%) children were prescribed antibiotics at the time of discharge (hospital median, 30.0%; range, 0%-76.0%; $P < .001$) (Figure 2). Of children who received postoperative antibiotics, 532 (92.8%) received intravenous antibiotics on postoperative day 1 with the most common regimens being piperacillin-tazobactam

Table. Demographic Characteristics and Measures of Disease Severity in Children With Nonperforated Appendicitis With Gangrenous, Suppurative, and/or Exudative Findings Who Did and Did Not Receive Postoperative Antibiotics Before and After Propensity Score Matching

Variable	Entire cohort			Propensity matched cohort ^a		
	Postoperative antibiotics (n = 573)	No postoperative antibiotics (n = 385)	P value	Postoperative antibiotics (n = 202)	No postoperative antibiotics (n = 202)	P value
Age at operation, mean (SD), y	10.5 (3.8)	11.1 (3.5)	.02	10.9 (3.8)	11.1 (3.7)	.66
Gangrene present, No. (%)	347 (60.6)	115 (29.9)	<.001	72 (35.6)	72 (35.6)	>.99
Postoperative length of stay, No. (%)						
0 d	20 (3.5)	187 (48.6)	<.001	20 (9.9)	20 (9.9)	>.99
1 d	229 (40.0)	187 (48.6)		171 (84.7)	171 (84.7)	
2 d	175 (30.5)	10 (2.6)		10 (5.0)	10 (5.0)	
≥3 d	149 (26.0)	1 (0.3)		1 (0.5)	1 (0.5)	
Operative duration, median (IQR), min	46 (35-64)	41 (32-53)	<.001	45 (36-59)	44 (35-54)	.19

^a Matched on age at operation, presence (or absence) of gangrene, and postoperative length of stay.

Figure 2. Variation in Hospital-Level Postoperative Antibiotic Use and Surgical Site Infection Rates



(190 [35.7%]; hospital median, 9.1%; range, 0%-93.9%), ceftriaxone with metronidazole (185 [34.8%]; hospital median, 46.5%; range, 0%-89.5%), cefoxitin (73 [13.7%]; hospital median, 0%; range, 0%-32.9%), ertapenem (30 [5.6%]; hospital median, 0%; range, 0%-62.8%), and ciprofloxacin with metronidazole (22 [4.1%]; hospital median, 4.2%; range, 0%-18.5%). The most common antibiotics prescribed at discharge were amoxicillin-clavulanic acid (174 [54.5%]; hospital median, 84.4%; range, 5.0%-100%) and ciprofloxacin with metronidazole (129 [40.4%]; hospital median, 0%; range, 0%-92.5%). The median (IQR) duration of postoperative antibiotics for all patients was 1 (0-6) day and ranged from 0 to 7 days across hospitals ($P < .001$) (Figure 3).

SSIs

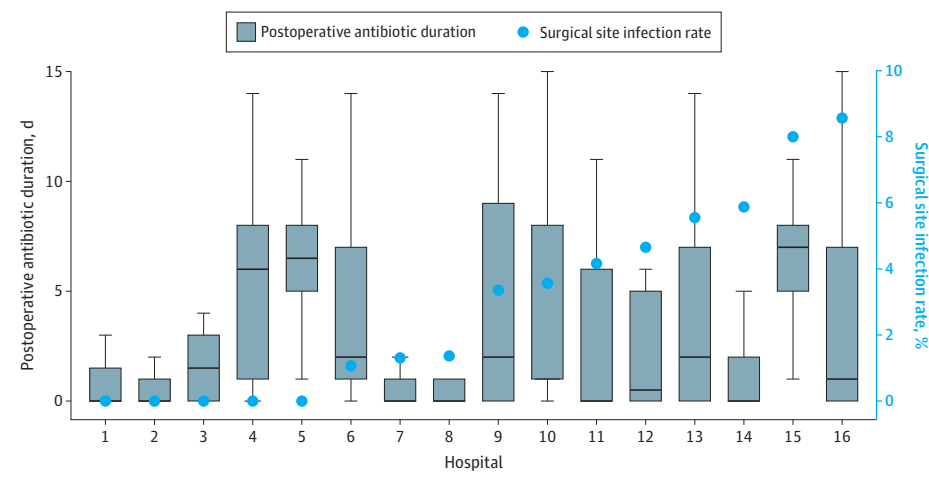
The overall postoperative SSI rate was 2.8% (27 of 958; incisional SSI rate, 1.5% [14 of 958]; organ space infection rate, 1.4% [13 of 958]) and ranged from 0% to 8.6% across hospitals. Hospital-level O/E ratios for SSI rates ranged from 0 to 1.28. There was no correlation between hospital-level rates of SSI and postoperative antibiotic use rates (hospital median, 53.6%; range: 31.6%-100%; Spearman $\rho = -0.10$; $P = .71$) (Figure 2) or mean postoperative antibiotic duration (hospital median, 1 day; range: 0-7 days; Spearman $\rho = -0.07$; $P = .79$) (Figure 3).

Before matching, SSI rates were similar between children who did and did not receive postoperative antibiotics (any SSI: 19 of 573 [3.3%] vs 8 of 385 [2.1%], $P = .26$; incisional SSI: 9 of 573 [1.6%] vs 5 of 385 [1.3%], $P = .73$; organ space SSI: 10 of 573 [1.8%] vs 3 of 385 [0.8%], $P = .21$). In the propensity-matched cohort including 404 patients, the overall SSI rate was 1.7% (7 of 404) and rates remained similar between groups after adjustment for clustering (3 of 202 [1.5%] vs 4 of 202 [2.0%]; OR, 0.75; 95% CI, 0.16-3.39; overall $P = .70$) (Figure 4). When stratified by incisional vs organ space SSI, there remained no significant difference between those who did and did not receive postoperative antibiotics (incisional: 3 of 202 [1.5%] vs 2 of 202 [1.0%], $P = .65$; organ space: 0% vs 2 of 202 [1.0%], $P = .16$).

Abdominal Imaging

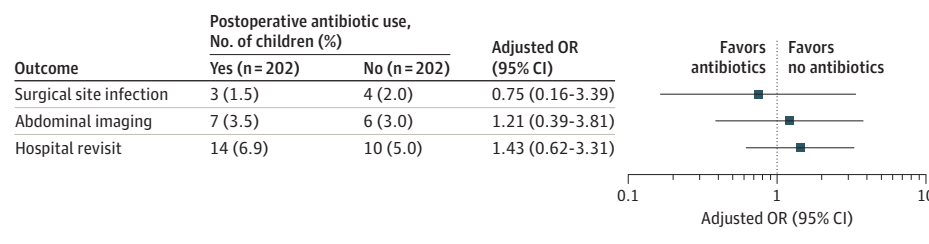
The overall rate of postoperative abdominal imaging use was 5.6% (54 of 958), which ranged from 0% to 28.0% across hospitals. Hospital-level O/E ratios for imaging use ranged from 0.48 to 2.64. There was no correlation between hospital-level O/E ratios of imaging use and postoperative antibiotic use rates (Spearman $\rho = -0.35$; $P = .18$) or mean empirical postoperative antibiotic duration (Spearman $\rho = -0.20$; $P = .46$).

Figure 3. Variation in Hospital-Level Postoperative Antibiotic Duration and Surgical Site Infection Rates



Hospital-level variation in postoperative surgical site infection rates (blue circles) and empirical postoperative antibiotic duration with IQR and absolute range represented by box plots in children with gangrenous, suppurative, or exudative nonperforated appendicitis from 16 children's hospitals. Hospitals are ordered from left to right by increasing rate of postoperative surgical site infection.

Figure 4. Postoperative Antibiotic Use and Outcomes



Postoperative outcomes in a propensity matched cohort of children with gangrenous, suppurative, or exudative nonperforated appendicitis who did and did not receive postoperative antibiotics.

Before matching, imaging rates were higher in children treated with postoperative antibiotics compared with those who were not (44 of 573 [7.7%] vs 10 of 385 [2.6%]; $P < .001$). After propensity score matching, imaging rates of use were similar between treatment groups after adjusting for hospital-level clustering (Figure 4).

Postdischarge Hospital Revisits

The overall revisit rate was 7.1% (68 of 958), which ranged from 0% to 16.0% across hospitals. Hospital-level O/E ratios for revisit rates ranged from 0.99 to 1.02. There was no correlation between hospital-level O/E ratios of revisits and postoperative antibiotic rates of use (Spearman $\rho = 0.16$; $P = .55$) or mean postoperative duration (Spearman $\rho = 0.21$; $P = .42$).

Before matching, revisit rates were 8.4% (48 of 573) in children treated with postoperative antibiotics and 5.2% (20 of 385) in those who were not ($P = .06$). After propensity score matching, revisit rates were similar between treatment groups after adjusting for hospital-level clustering (Figure 3).

Discussion

In this multicenter propensity-matched cohort study of children from 16 hospitals, postoperative continuation of antibiotics was not associated with improved outcomes in cases of nonperforated appendicitis with GSE findings. Rates of SSI were no different in children who received postoperative antibiotics

compared with those who did not, and no correlation was found between increasing use or duration of postoperative antibiotics and SSI rates at the hospital level. Furthermore, use of postoperative antibiotics was not associated with lower rates of postoperative abdominal imaging use or hospital revisits.

To our knowledge, this study represents the first multicenter analysis to evaluate the association between postoperative antibiotic use and outcomes in children with nonperforated appendicitis with GSE findings. Previous data are limited to a small, single-center analysis of 69 children with gangrenous appendicitis where no difference in SSI rates was found between children who received and did not receive postoperative antibiotics.¹⁰ The present study represents a more robust and generalizable analysis due to its multicenter design, relatively large sample size, and use of previously validated intraoperative criteria for nonperforated appendicitis with GSE findings.⁹ Furthermore, the validity of this analysis is strengthened by the use of propensity matching to balance measures of disease severity between treatment groups. Finally, inclusion of a complementary hospital-level analysis provides further insight into the lack of clinical effectiveness of postoperative antibiotic use over a wide range of practice variation as it pertains to both use and duration as separate measures.

The results of this analysis have important implications for optimizing antimicrobial stewardship in the treatment of children with nonperforated appendicitis associated with GSE findings. Overuse of antibiotics has been associated with

increased risk of *Clostridium difficile* infection, acute kidney injury, and adverse events including anaphylaxis.^{17,18} Furthermore, prolonged antibiotic treatment has been identified as a major driver of antimicrobial resistance.^{6,7,19} It is important to emphasize that surgical site infections were rare in this cohort of children whether or not postoperative antibiotics were used, and continuation of antibiotics postoperatively was not associated with a clinically meaningful reduction in SSI rates. When considering that over one-half of the children in this analysis received postoperative antibiotics, abandonment of this practice could result in a considerable reduction in antibiotic use in children with nonperforated appendicitis with GSE findings, particularly at hospitals that continue antibiotics for multiple days postoperatively. Furthermore, the results of this analysis may also challenge the utility (as well as the increased resource use and cost) of clinical pathways mandating inpatient admission to give intravenous postoperative antibiotics in children with GSE findings when they would otherwise meet clinical criteria for discharge.¹¹⁻¹³

Limitations

The results of this study must be interpreted in the context of its limitations. Data were retrospectively collected, and errors in misclassification were possible despite use of rigorous and standardized data collection methods. Another potential limitation is confounding by indication, where children with more severe disease may be more likely to receive postoperative antibiotics. Several strategies were used to mitigate this potential bias, including propensity matching based on disease severity and use of a complementary hospital-level analysis to

explore outcomes over a wide range of postoperative antibiotic use practices. Despite the wide variation in antibiotic use, SSIs were infrequent, with nearly one-third of hospitals reporting no SSIs during the study period. The analysis may, therefore, have been underpowered to detect statistical differences between groups given the exceedingly low event rates (whether or not postoperative antibiotics were used), although the 0.5% absolute difference in SSI rates between groups may have limited clinical significance. Finally, lack of correlation in the hospital-level analysis between SSI rates and postoperative antibiotic use on the basis of both rate and duration of use provides further compelling evidence against any benefit with extended antibiotic treatment. When considering the broad range in median postoperative antibiotic duration across hospitals, lack of correlation between duration and SSI rates would also argue against the existence of any threshold of postoperative treatment days needed for SSI reduction.

Conclusions

The results of this cohort study suggest that postoperative antibiotics should not be used in children with nonperforated appendicitis with GSE findings. When considering the potential magnitude of national practice variation in the use of postoperative antibiotics that can be extrapolated from these data, elimination of postoperative antibiotic use in children with nonperforated appendicitis with GSE findings could substantially improve antimicrobial stewardship in the management of pediatric appendicitis.

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Data Sharing Statement: See [Supplement 2](#).

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Invited Commentary

Antibiotic Use in Gangrenous, Suppurative, or Exudative Appendicitis

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Appendicitis is one of the most common indications for nonelective surgery in children, and there is significant variation in resource use including antibiotic duration.¹ The postoperative management of acute appendicitis is highly dependent on the surgeon's intraoperative

classification of the severity of the inflammation, which ranges from mild inflammation to frank perforation. Given the increased risk of surgical site infection (SSI) with perforated appendicitis, postoperative antibiotics are standard of care. For simple appendicitis, on the other hand, no postoperative antibiotics are indicated, and embracing this concept has led to significant decreases in resource use with growing numbers of institutions doing same-day discharge.² Gangrenous, suppurative, and exudative (GSE) appendicitis represents a middle zone of severe inflammation without frank perforation and is classified as uncomplicated according to the American College of Surgeons National Surgical Quality Improvement Program-Pediatric (NSQIP-Pediatric) definition. Complicated appendicitis must meet at least 1 of the following criteria: visible hole in the appendix, fecalith outside the appendix, abscess, or diffuse fibrinopurulent exudate throughout the abdominal cavity. Single-institution studies have supported the notion that GSE appendicitis can

be treated as uncomplicated (no postoperative antibiotics) without increasing SSI rates^{3,4}; however, these findings have not been embraced widely.^{5,6}

In this issue of *JAMA Surgery*, Cramm and colleagues⁷ report the first, large, multicenter study demonstrating that postoperative antibiotics do not reduce risk of SSI in patients with GSE appendicitis. They used NSQIP-Pediatric data supplemented by medical record review from 16 centers to compare SSI rates in children with uncomplicated, GSE appendicitis who did and did not receive postoperative antibiotics.⁷ Of 958 patients with GSE appendicitis, 60% received postoperative antibiotics. There was no association between postoperative antibiotic use and hospital-level SSI rates. In addition, propensity score-matched patient-level analysis revealed no differences in SSI rates (including both superficial and organ space SSI) for those who did or did not receive postoperative antibiotics (3.3% vs 2.1%; $P = .26$). These findings support the conclusions of prior studies: postoperative antibiotics are not indicated for uncomplicated appendicitis, even if GSE findings are present. Treating GSE appendicitis as complicated appendicitis leads to overuse of antibiotics, increased risk of antimicrobial resistance, and excess length of stay. Cramm and colleagues⁷ have provided foundational evidence that should be incorporated into quality improvement initiatives to translate this knowledge into practice.



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