

Extended- Versus Narrower-Spectrum Antibiotics for Appendicitis

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abstract

BACKGROUND AND OBJECTIVES: Appendicitis guidelines recommend either narrower- or extended-spectrum antibiotics for treatment of complicated appendicitis. The goal of this study was to compare the effectiveness of extended-spectrum versus narrower-spectrum antibiotics for children with appendicitis.

METHODS: We performed a retrospective cohort study of children aged 3 to 18 years discharged between 2011 and 2013 from 23 freestanding children's hospitals with an appendicitis diagnosis and appendectomy performed. Subjects were classified as having complicated appendicitis if they had a postoperative length of stay ≥ 3 days, a central venous catheter placed, major or severe illness classification, or ICU admission. The exposure of interest was receipt of systemic extended-spectrum antibiotics (piperacillin \pm tazobactam, ticarcillin \pm clavulanate, ceftazidime, cefepime, or a carbapenem) on the day of appendectomy or the day after. The primary outcome was 30-day readmission for wound infection or repeat abdominal surgery. Multivariable logistic regression, propensity score weighting, and subgroup analyses were used to control for confounding by indication.

RESULTS: Of 24 984 patients, 17 654 (70.7%) had uncomplicated appendicitis and 7330 (29.3%) had complicated appendicitis. Overall, 664 (2.7%) patients experienced the primary outcome, 1.1% among uncomplicated cases and 6.4% among complicated cases ($P < .001$). Extended-spectrum antibiotic exposure was significantly associated with the primary outcome in complicated (adjusted odds ratio, 1.43 [95% confidence interval, 1.06 to 1.93]), but not uncomplicated, (adjusted odds ratio, 1.32 [95% confidence interval, 0.88 to 1.98]) appendicitis. These odds ratios remained consistent across additional analyses.

CONCLUSIONS: Extended-spectrum antibiotics seem to offer no advantage over narrower-spectrum agents for children with surgically managed acute uncomplicated or complicated appendicitis.



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DOI: 10.1542/peds.2015-4547

WHAT'S KNOWN ON THIS SUBJECT: Overuse of extended-spectrum antibiotics contributes to antibiotic resistance. Appendicitis is a leading condition contributing to antibiotic use in children's hospitals. Whether extended-spectrum antibiotics offer a therapeutic advantage over narrower spectrum agents for children with acute appendicitis remains unclear.

WHAT THIS STUDY ADDS: Approximately 2.7% of children who had undergone appendectomy experienced 30-day readmissions for wound infections or second abdominal surgical procedures. Extended-spectrum antibiotic treatment was not associated with lower readmission rates and is therefore likely unnecessary, especially for those with uncomplicated appendicitis.

To cite: Kronman MP, Oron AP, Ross RK, et al. Extended- Versus Narrower-Spectrum Antibiotics for Appendicitis. *Pediatrics*. 2016;138(1):e20154547

Appendicitis is 1 of the 4 leading conditions contributing to antibiotic use in children's hospitals.¹ Antibiotic recommendations for patients with appendicitis depend on whether the appendicitis is complicated, defined as presence of perforation, gangrene, peritonitis, or abscess formation. For uncomplicated appendicitis, guidelines recommend the use of relatively narrow-spectrum antibiotics such as cefoxitin, cefotetan, or cefazolin with metronidazole for perioperative prophylaxis.² Patients with complicated appendicitis, however, require treatment of complicated intra-abdominal infections. Although the guidelines for complicated intra-abdominal infections in adults state that narrower-spectrum regimens are "preferable to regimens with substantial antipseudomonal activity," pediatric recommendations are less definitive; narrower-spectrum regimens (eg, cefoxitin) and extended-spectrum regimens (eg, piperacillin/tazobactam) are listed as equivalent choices for children with community-acquired, complicated intra-abdominal infections, including ruptured appendicitis.³ Furthermore, extended-spectrum antibiotic use increases antimicrobial resistance,⁴ and resistant infections are associated with increased morbidity, mortality, and health care costs.⁵⁻⁷

Appendicitis is a high-priority condition for pediatric comparative effectiveness studies.⁸ Readmission after appendicitis is common, costly, important to quality improvement interventions, and can occur due to postoperative complications.^{9,10} Although illness severity and insurance status are identified risk factors for all-cause readmission after appendicitis, the comparative effectiveness of extended- versus narrower-spectrum antibiotics for preventing appendicitis complications is not established.¹¹ If extended-spectrum therapy offers no advantage for this common

condition, reducing unnecessary use of these agents would provide an important target for antimicrobial stewardship efforts. Thus, the goal of the present study was to compare the effectiveness of empiric extended-spectrum antibiotics versus narrower-spectrum antibiotics for preventing short-term appendicitis complications in children.

METHODS

Data Source

A retrospective cohort study was performed in pediatric inpatients with appendicitis by using the Pediatric Health Information System (PHIS) database, which contained data from 47 US freestanding children's hospitals at study data extraction. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS) and represent 17 of the 20 major metropolitan areas nationwide. PHIS provides de-identified discharge and encounter data, including demographic characteristics, diagnoses, procedures, and resource utilization data (eg, pharmaceuticals), but it contains no microbiology culture data. Data quality and reliability are assured through joint efforts between Children's Hospital Association and participating hospitals.

Inclusion Criteria

Children aged 3 to 18 years discharged from PHIS hospitals between January 1, 2011, and December 31, 2013, were included. Because making a timely diagnosis of appendicitis is difficult in young children, children aged <3 years were not included. Sample size calculations assumed 9000 PHIS admissions for appendicitis annually; 50% to 75% of patients would receive extended-spectrum antibiotics; and readmission for surgery or wound infection could occur in 1% to 10%.^{11,12} Given these assumptions,

a 3-year study period would provide 80% power to detect odds ratios of the association between extended-spectrum antibiotic exposure and these readmissions ranging as low as 1.1 to 1.4.

Patients with *International Classification of Diseases, Ninth Revision, Clinical Modification* primary diagnosis codes for acute or unqualified appendicitis (540.0, 540.1, 540.9, or 541)¹¹ and with an appendectomy performed (because the ~4% of appendicitis patients managed nonoperatively represent a different population) were included.¹¹ To avoid sampling bias by classification differences across hospitals, patients classified as inpatient, observation, or ambulatory surgery hospitalized overnight (ie, with a length of stay [LOS] ≥1 day) were included.

Exclusion Criteria

Patients hospitalized with appendicitis in the previous 12 months, those with complex chronic conditions,¹³ those who died during the index visit (and could not experience readmission), those transferred from another institution and lacking an emergency department charge (in whom antibiotic exposure capture might be incomplete), and those admitted to hospitals with incomplete or unreliable pharmacy or covariate data were excluded. We also excluded patients who did not receive antibiotics on the day of their appendectomy or the day after (which suggested missing antibiotic exposure data rather than a clinical decision to withhold antibiotics). PHIS hospitals without ambulatory surgical data ($n = 10$), incomplete pharmacy data ($n = 7$), or >10% missing data for race/ethnicity or payer ($n = 7$) were excluded, leaving 23 hospitals. In this group, admission type was most commonly inpatient (62.1%), followed by observation

(29.7%) and ambulatory surgery (8.2%).

Exposure of Interest

Antibiotic exposures were identified by using billing charges according to generic drug name and day of service for systemic (oral or parenteral) antibacterial agents. Extended-spectrum antibiotics were defined as guideline-recommended agents with substantial activity against *Pseudomonas aeruginosa* or other highly resistant Gram-negative bacteria: piperacillin ± tazobactam, ticarcillin ± clavulanate, ceftazidime, cefepime, imipenem, meropenem, or ertapenem. Exposure to empiric extended-spectrum antibiotics was defined according to receipt of any extended-spectrum antibiotic on the day of the patient's appendectomy or the next day; otherwise, they were defined as exposed to narrower-spectrum antibiotics.

Outcome of Interest

The primary outcome was treatment failure, defined as inpatient readmission for a second abdominal surgical procedure, percutaneous drainage (eg, by interventional radiology), wound infection, or other complication (eg, bowel obstruction) within 30 days. Readmissions for other reasons were not included. To ensure primary outcomes were not missed, 1 author (Dr Kronman) reviewed all primary diagnosis and procedure codes for all patients readmitted within 30 days (blinded to exposure status) and included all relevant codes in the outcome of interest definition (Supplemental Table 5).

Appendicitis Classification

Previous administrative data definitions of uncomplicated and complicated appendicitis correlate with readmission risk.^{10,11} These definitions were modified to be more conservative, defining uncomplicated appendicitis as

those episodes with overall LOS ≤2 days and complicated appendicitis as those with postoperative LOS ≥3 days, procedure codes for peripherally inserted central catheter placement (indicating need for prolonged antimicrobial therapy), admission to the ICU, or who were in either of the top 2 All Patient Refined Diagnosis-Related Group Severity of Illness score quartiles. Patients with overall LOS ≥3 days but postoperative LOS ≤2 days ($n = 956$) were excluded because this group is difficult to classify as uncomplicated or complicated with the use of administrative data alone. Analyses were stratified according to complicated versus uncomplicated cases (termed "appendicitis complication status").

Primary Analyses

Antibiotic use was summarized according to exposure type and complication status by using proportions, means, and medians. Multivariable models adjusted for age (3–5 years, 6–11 years, and 12–18 years), sex, race/ethnicity, payer (government, employer, or other), presence of peripherally inserted central catheters (for complicated appendicitis only), and All Patient Refined Diagnosis-Related Group Severity of Illness score. LOS was treated as a binary variable (2 days vs 1 day for uncomplicated appendicitis; ≥7 days vs <7 days for complicated appendicitis).

At the study outset, 2 major types of potential confounding that might threaten the validity of our findings were targeted. The first addressed potential confounding by hospital, in which given hospitals may be more likely to use certain antibiotics and experience certain (better or worse) outcomes. The second addressed potential confounding by indication, in which sicker patients were more likely to receive extended-spectrum antibiotics and to have a higher baseline risk of complications.

Furthermore, we expected a low treatment failure rate overall.

Two a priori planned primary analyses were conducted. First, we used multivariable logistic regression to identify the association between extended-spectrum antibiotic exposure and treatment failure, adjusting for admission hospital and the aforementioned covariates and stratifying according to complication status. Multivariable linear regression was next performed to determine the risk difference for the primary outcome, based on exposure. To determine whether the antibiotic effect differed between those with uncomplicated and complicated appendicitis, the cohort was then evaluated without stratification and included an interaction term between the antibiotic exposure type and appendicitis complication status. Lastly, the operative approach (comparing those with procedure codes for laparoscopic appendectomy versus all others) was included in the model to evaluate whether operative approach was associated with the primary outcome.

Because propensity score adjustment has advantages in the situations of low outcome rates and potential confounding,¹⁴ the second planned analysis included a propensity score model. In this model, the propensity score estimated a given patient's likelihood of receiving extended-spectrum antibiotics based on other measured covariates, and was compared only versus other patients at the same hospital. The inverse of the propensity score was then used to up- or down-weight patients within each hospital to make the propensity score-weighted exposed and unexposed groups more alike in their baseline covariate distribution and help address confounding both by indication and by hospital.¹⁵ Propensity scores were truncated at the 99.9 percentile. Multivariable logistic regression was then

performed, weighting each patient by this inverse probability.

Secondary Analyses

To evaluate the robustness of the findings, several subanalyses were performed, taking advantage of antibiotic usage patterns across the included hospitals. Because certain hospitals might have incorporated a balanced use of both antibiotic types, antibiotic selection at these centers might be highly driven by illness severity. At these hospitals, confounding by indication would remain, although confounding by hospital would be less prominent. Of the 23 included hospitals, 14 had an extended-spectrum exposure rate between 10% and 90%; these hospitals used both extended-spectrum and narrower spectrum antibiotics at least occasionally. In this group, called the “restricted cohort with variation in prescribing,” the primary analysis was repeated, stratified according to complication status.

Alternatively, certain hospitals might use 1 antibiotic type almost exclusively, suggesting that these hospitals performed limited decision-making regarding antibiotic selection by illness severity. At these hospitals, confounding by indication would be less prominent, although confounding by hospital would remain. Of the 23 included hospitals, 6 used extended-spectrum antibiotics almost always and 6 used them almost never, regardless of appendicitis complication status (Fig 1). The remaining 11 hospitals used either extended-spectrum antibiotics almost always for complicated appendicitis and almost never for uncomplicated appendicitis (6 hospitals), or they fit no pattern (5 hospitals). In a separate subanalysis, the primary analysis was repeated, stratified according to complication status, including a hospital group covariate based on each hospital’s pattern of extended-spectrum

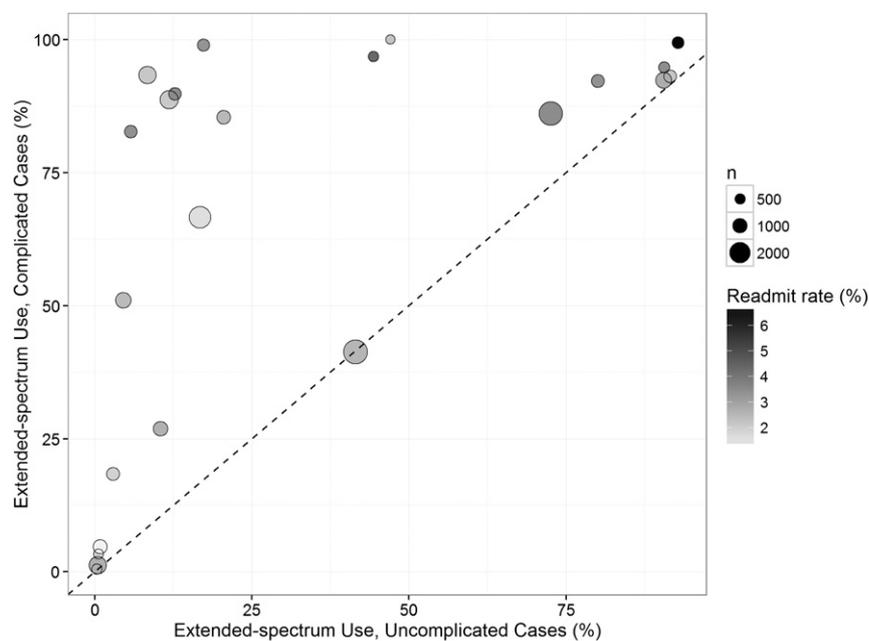


FIGURE 1

Proportion of patients with appendicitis receiving extended-spectrum antibiotics according to hospital and complication status. The axes represent the proportional extended-spectrum antibiotic use among uncomplicated (x-axis) and complicated (y-axis) appendicitis cases at each hospital. Each circle represents 1 hospital, scaled to demonstrate the relative proportion of overall appendicitis cases contributed by that hospital. The dashed line represents equal extended-spectrum use between complicated and uncomplicated cases.

prescribing (almost always, almost never, complicated appendicitis only, or other). If hospital groups predicted treatment failure better than antibiotic exposure, this approach would implicate confounding by hospital as a strong driver of any association between antibiotic exposure and treatment failure.

Lastly, a subanalysis to address the possibility of disease misclassification among those with complicated appendicitis was performed. In this subanalysis, the primary analysis was repeated in the subgroup of patients with complicated appendicitis who only received antibiotic regimens that were guideline-recommended specifically for the treatment of complicated intra-abdominal infections.³

R version 3.1.0 (R Core Team, Vienna, Austria) was used for all analyses. We considered a 2-tailed *P* value <.05 to be significant. This study was approved by the Seattle Children’s Hospital Institutional Review Board.

RESULTS

Cohort and Antibiotic Use

Overall, 28 826 children had appendicitis and underwent an appendectomy at 23 hospitals. After exclusions, the final cohort contained 24 984 patients, representing 86.7% of all appendicitis cases at those hospitals, with a median of 780 cases per hospital (interquartile range, 648–1455; range, 372–2801). Appendectomies were performed on the first or second hospital day in 24 875 (99.6%) patients, and 17 654 (70.7%) patients had uncomplicated appendicitis (Table 1). The hospital-level median empiric extended-spectrum antibiotic exposure rate was 42.7%, ranging across hospitals from 0.4% to 94.6%. Overall, empiric extended-spectrum antibiotic exposure occurred in 5841 (33.1%) uncomplicated cases and in 4835 (66.0%) complicated cases. Operative approach was laparoscopic in 16 760 (94.9%) of uncomplicated cases

TABLE 1 Patient Demographic Characteristics According to Appendicitis Complication Status and Exposure Group

Characteristic	Uncomplicated Appendicitis			Complicated Appendicitis			Overall Study Total (N = 24 984)
	Extended-Spectrum Exposed (n = 5841)	Narrower-Spectrum Exposed (n = 11 813)	Total (N = 17 654)	Extended-Spectrum Exposed (n = 4835)	Narrower-Spectrum Exposed (n = 2495)	Total (N = 7330)	
Female sex	2190 (37.5)	4685 (39.7)	6875 (38.9)	1913 (39.6)	1009 (40.4)	2922 (39.9)	9797 (39.2)
Age, y							
3–5	396 (6.8)	802 (6.8)	1198 (6.8)	838 (17.3)	455 (18.2)	1293 (17.6)	2491 (10.0)
6–11	2916 (49.9)	5817 (49.2)	8733 (49.5)	2502 (51.7)	1318 (52.8)	3820 (52.1)	12 553 (50.2)
12–18	2529 (43.3)	5194 (44.0)	7723 (43.7)	1495 (30.9)	722 (28.9)	2217 (30.2)	9940 (39.8)
Insurance							
Employer	3133 (53.6)	5875 (49.7)	9008 (51.0)	2038 (42.2)	920 (36.9)	2958 (40.4)	11 966 (47.9)
Government	2440 (41.8)	5452 (46.2)	7892 (44.7)	2548 (52.7)	1445 (57.9)	3993 (54.5)	11 885 (47.6)
Self	195 (3.3)	362 (3.1)	557 (3.2)	194 (4.0)	84 (3.4)	278 (3.8)	835 (3.3)
Other/unknown	73 (1.2)	124 (1.0)	197 (1.1)	55 (1.1)	46 (1.8)	101 (1.4)	298 (1.2)
Race/ethnicity							
White	2935 (50.2)	6379 (54.0)	9314 (52.8)	1985 (41.1)	995 (39.9)	2980 (40.7)	12 293 (49.2)
Latino	1879 (32.2)	3718 (31.5)	5597 (31.7)	1901 (39.3)	1103 (44.2)	3004 (41.0)	8601 (34.4)
Black	536 (9.2)	768 (6.5)	1304 (7.4)	485 (10.0)	164 (6.6)	649 (8.9)	1953 (7.8)
All other	491 (8.4)	948 (8.0)	1439 (8.2)	464 (9.6)	233 (9.3)	697 (9.5)	2136 (8.5)
ICU admission	NA	NA	NA	111 (2.3)	33 (1.3)	144 (2.0)	144 (0.6)
LOS ^a	1 (1–2)	1 (1–2)	1 (1–2)	5 (4–7)	5 (4–6)	5 (4–6)	1 (1–3)
Severity of illness							
Minor	4884 (83.6)	10 417 (88.2)	15 301 (86.7)	498 (10.3)	350 (14.0)	848 (11.6)	16 149 (64.6)
Moderate	957 (16.4)	1396 (11.8)	2353 (13.3)	4066 (84.1)	2036 (81.6)	6102 (83.2)	8455 (33.8)
Major	NA	NA	NA	221 (4.6)	91 (3.6)	312 (4.3)	312 (1.2)
Extreme	NA	NA	NA	50 (1.0)	18 (0.7)	68 (0.9)	68 (0.3)
Primary outcome	88 (1.5)	104 (0.9)	192 (1.1)	346 (7.2)	126 (5.1)	472 (6.4)	664 (2.7)

Data are presented as n (column %) unless otherwise indicated. NA, not applicable.

^a Presented as days (interquartile range).

TABLE 2 Most Common Antibiotic Regimens Among Narrower-Spectrum and Extended-Spectrum Antibiotic-Exposed Subjects With Uncomplicated Appendicitis

Antibiotic Regimen	Narrower-Spectrum Exposed		Extended-Spectrum Exposed	
	N (%)	N (%)	N (%)	N (%)
Cefoxitin	5413 (45.8)	—	Piperacillin/tazobactam	5188 (88.8)
Ceftriaxone + metronidazole	1664 (14.1)	—	Ertapenem	529 (9.1)
Ampicillin/sulbactam + metronidazole	1041 (8.8)	—	Meropenem	96 (1.6)
Cefotetan	845 (7.2)	—	Piperacillin/tazobactam + ertapenem	11 (0.2)
Ceftriaxone	833 (7.1)	—	Ceftazidime	6 (0.1)
Clindamycin + gentamicin	316 (2.7)	—	All other regimens	11 (0.2)
Cefazolin + cefoxitin	169 (1.4)	—	—	—
Ampicillin/sulbactam	165 (1.4)	—	—	—
Cefoxitin + ceftriaxone + metronidazole	154 (1.3)	—	—	—
Cefoxitin + other	114 (1.0)	—	—	—
All other regimens	1099 (9.3)	—	—	—

—, not applicable.

and 6641 (90.6%) of complicated cases. Tables 2 and 3 list the most commonly used antibiotic regimens.

Treatment failure occurred in 664 (2.7%) patients overall, 1.1% among uncomplicated cases and 6.4% among complicated cases ($P < .001$). Within both uncomplicated and complicated appendicitis groups, the proportion of patients experiencing

both treatment failure overall and each subcategory of treatment failure was consistently higher among those receiving extended-spectrum antibiotics in unadjusted analyses (Table 1, Supplemental Table 6).

Primary Adjusted Analyses

Among patients with uncomplicated appendicitis, empiric

extended-spectrum antibiotic exposure was moderately, but not significantly, associated with treatment failure (adjusted odds ratio [aOR], 1.32 [95% confidence interval (CI), 0.88 to 1.98] (Table 4); adjusted risk difference, 0.3% [95% CI, -0.1 to 0.8]) (Supplemental Table 7). Propensity score weighting balanced the majority of covariates in

TABLE 3 Most Common Antibiotic Regimens Among Narrower-Spectrum and Extended-Spectrum Antibiotic-Exposed Subjects With Complicated Appendicitis

Narrower-Spectrum Exposed		Extended-Spectrum Exposed	
Antibiotic Regimen	N (%)	Antibiotic Regimen	N (%)
Ceftriaxone + metronidazole	945 (37.9)	Piperacillin/tazobactam	4127 (85.4)
Ampicillin/sulbactam + metronidazole	341 (13.7)	Ertapenem	381 (7.9)
Cefoxitin	316 (12.7)	Meropenem	261 (5.4)
Cefoxitin + metronidazole	165 (6.6)	Ceftazidime	30 (0.6)
Cefoxitin + ceftriaxone + metronidazole	93 (3.7)	Piperacillin/tazobactam + ertapenem	18 (0.4)
Cefazolin + ceftriaxone + metronidazole	92 (3.7)	Piperacillin/tazobactam + meropenem	12 (0.2)
Clindamycin + gentamicin	86 (3.4)	All other regimens	6 (0.1)
Cefotetan	60 (2.4)	—	—
Ampicillin/sulbactam	35 (1.4)	—	—
Ampicillin/sulbactam + ampicillin + gentamicin + metronidazole	35 (1.4)	—	—
All other regimens	327 (13.1)	—	—

—, not applicable.

TABLE 4 Primary and Subgroup Analyses of the Association Between Exposure to Extended-Spectrum Antibiotics and Readmission for Second Surgical Procedure or Wound Infection, Grouped According to Appendicitis Complication Status

Analytic Model	Rationale	Adjusted ^a Odds Ratio (95% CI) of Treatment Failure Based on Extended-Spectrum Antibiotic Exposure	
		Patients With Uncomplicated Appendicitis	Patients With Complicated Appendicitis
Unadjusted association	NA	1.72 (1.30 to 2.29)	1.45 (1.18 to 1.79)
Primary: multivariable logistic regression model	Primary adjusted model	1.32 (0.88 to 1.98)	1.43 (1.06 to 1.93)
Primary: propensity-score weighted model	Addresses confounding by indication and by hospital most efficiently	1.39 (1.14 to 1.71)	1.35 (1.17 to 1.55)
Secondary: restricted cohort with variation in prescribing	Addresses confounding by hospital	1.33 (0.86 to 2.04)	1.30 (0.95 to 1.79)
Secondary: accounting for hospital groups (always-versus never-using extended-spectrum antibiotics)	Addresses confounding by indication	1.42 (0.96 to 2.10)	1.42 (1.07 to 1.88)
Secondary: subgroup with guideline-recommended regimens for treatment of complicated appendicitis	Addresses misclassification of underlying disease	NA	1.31 (0.94 to 1.82)

NA, not applicable.

^a The first row displays the unadjusted odds ratio. Additional analyses were adjusted for age, sex, race, payer, severity of illness score, LOS, placement of a peripherally inserted central catheter (for complicated cases), and hospital. The narrower-spectrum exposed group is the reference group for all analyses.

the exposed and unexposed groups (Supplemental Table 8), and empiric extended-spectrum antibiotic exposure was significantly associated with treatment failure in the propensity score-weighted model (aOR, 1.39 [95% CI, 1.14 to 1.71]).

Among patients with complicated appendicitis, empiric extended-spectrum antibiotic exposure was significantly associated with treatment failure (aOR, 1.43 [95% CI, 1.06 to 1.93]) (Table 4). This finding represented a 1.9% increase in absolute risk of treatment failure (adjusted risk difference, 1.9% [95% CI, 0.2 to 3.5]). The odds of treatment failure were similar in the propensity

score-weighted model (aOR, 1.35 [95% CI, 1.17 to 1.55]).

When evaluating the entire, unstratified cohort, the effect of empiric extended-spectrum antibiotics did not differ between uncomplicated and complicated appendicitis cases (ie, no effect modification was present, $P = .8$), and empiric extended-spectrum antibiotic exposure remained associated with treatment failure (aOR, 1.42 [95% CI, 1.03 to 1.95]). A nonlaparoscopic operative approach was not associated with treatment failure in either uncomplicated (aOR, 1.62 [95% CI, 0.86 to 3.06]) or complicated (aOR, 1.18 [95% CI, 0.85 to 1.64]) appendicitis.

Secondary Adjusted Analyses

In the restricted hospital cohort with variation in prescribing, the association between empiric extended-spectrum antibiotic exposure and treatment failure was attenuated in both uncomplicated and complicated appendicitis groups, and was no longer statistically significant for the latter (aOR, 1.30 [95% CI, 0.95 to 1.79]) (Table 4).

In the analysis comparing hospital groups, empiric extended-spectrum antibiotic exposure remained moderately associated with treatment failure in both the uncomplicated and complicated appendicitis groups, but the association was significant only

for patients with complicated appendicitis (aOR in uncomplicated cases, 1.42 [95% CI, 0.96 to 2.10]; aOR in complicated cases, 1.42 [95% CI, 1.07 to 1.88]). However, after adjustment for antibiotic exposure type, patients at hospitals that almost always used empiric extended-spectrum antibiotics were no more likely to experience treatment failure (aOR in uncomplicated cases, 1.28 [95% CI, 0.75 to 2.17]; aOR in complicated cases, 1.02 [95% CI, 0.71 to 1.46]) than those at hospitals that almost never used these antibiotics.

Lastly, among patients with complicated appendicitis, 81% of patients exposed to narrower spectrum antibiotics and 100% of patients exposed to extended-spectrum antibiotics received guideline-recommended antibiotic regimens (Table 3); the other 19% of patients exposed to narrower spectrum antibiotics received agents consistent with intra-abdominal infection treatment but which are not guideline-supported, such as ampicillin-sulbactam with metronidazole. Empiric extended-spectrum antibiotic exposure remained associated with treatment failure, but not statistically significantly so, among those with only guideline-recommended antibiotic regimens (aOR, 1.31 [95% CI, 0.94 to 1.82]).

DISCUSSION

Examining almost 25 000 children with appendicitis across 23 children's hospitals, use of empiric extended-spectrum antibiotics with activity against highly resistant Gram-negative bacteria was not associated with improved outcomes for this common condition. Among the subgroup with complicated appendicitis, however, use of empiric extended-spectrum antibiotics was associated with treatment failure.

The association between empiric extended-spectrum antibiotics and

treatment failure among children with complicated appendicitis may reflect residual confounding by indication if sicker patients received these agents. Multiple approaches were used to address this possibility. First, multivariable regression and propensity score-weighted modeling were performed to address confounding both by indication and by hospital. To pursue further confounding by hospital, analyses were repeated in the subgroup of patients from hospitals in which both extended-spectrum and narrower-spectrum antibiotic regimens were used. In addition, to focus on confounding by indication, patients at hospitals using narrower-spectrum regimens almost exclusively were compared with those at hospitals using extended-spectrum therapy almost exclusively. Finally, the complicated appendicitis cohort was limited to children given guideline-recommended therapy, to address possible disease misclassification. Although residual confounding cannot be entirely eliminated, results were consistent across all models but attenuated in some secondary analyses with smaller numbers. Furthermore, both the fact that there were clusters of freestanding US children's hospitals in which either almost all or almost no patients received extended-spectrum antibiotics, regardless of complication status (Fig 1), and that the likelihood of treatment failure did not differ between these hospital groups when accounting for antibiotic selection, suggest that hospital standard practice may drive antibiotic selection at these hospitals more than illness severity.

Extended-spectrum antibiotics typically provide coverage against *P aeruginosa* and other highly resistant Gram-negative organisms not covered by narrower spectrum antibiotics. The lack of observed benefit of extended-spectrum antibiotics suggests that these

organisms play a limited role in uncomplicated appendicitis. The observed increased treatment failure among complicated appendicitis cases treated with extended-spectrum antibiotics could be related to adverse events associated with the breadth of the antibiotic spectrum (eg, *Clostridium difficile* infection). Lastly, experimental models have shown that microbiota changes can adversely affect gut and skin wound healing,^{16,17} consistent with the association between use of microbiota-altering extended-spectrum antibiotics and postoperative complications.

These findings have antimicrobial stewardship implications. The optimal antibiotic management of appendicitis remains undefined; some single-agent, extended-spectrum regimens are associated with shorter LOS and lower hospital charges.¹² However, avoiding extended-spectrum antibiotics is preferable when possible, due both to increased cost and the association between their use and development of antibiotic-resistant infections.^{4,18} Furthermore, appendicitis is a top contributor to antibiotic use in hospitalized children.¹ Local guidelines have successfully standardized appendicitis care, suggesting that antimicrobial stewardship programs could support selecting narrower-spectrum antibiotics for children with appendicitis (and particularly uncomplicated appendicitis) whenever appropriate.^{19,20}

Strengths of the present study include the cohort size, exclusion of patients whose exposure or complication status was difficult to classify, and multiple subgroup analyses to explore the consistency of observed associations. This study also has limitations. With use of administrative data, there is the potential for misclassification of diagnosis, antibiotic exposure, and outcome based on variable

coding practices across hospitals. Misclassification was addressed by excluding hospitals with high rates of missing data, only including patients who stayed overnight and had an appendectomy performed, and excluding patients transferred from other hospitals. Because PHIS does not contain culture results, we could not determine whether extended-spectrum antibiotics were warranted for a subset of patients with complicated appendicitis. Treatment failures managed as an outpatient or at a different facility would be missed. Inpatient antibiotic selection and duration beginning ≥ 2 days after appendectomy were not evaluated; antibiotic selection, route, and duration after discharge were

unavailable in our data. Each of these factors could relate to the likelihood of treatment failure but would have to vary systematically according to initial antibiotic selection to affect the results. Lastly, PHIS hospitals represent only 15% of pediatric hospital admissions nationally, and we excluded approximately one-half of the PHIS hospitals for issues related to data availability and quality; thus, our findings may not be generalizable to other inpatient pediatric surgical settings.²¹

CONCLUSIONS

This large, multicenter study found no advantage of empiric extended-spectrum antibiotic therapy for

children with uncomplicated or complicated appendicitis. Given these findings and the frequency of extended-spectrum antibiotic use for this condition, pediatric appendicitis represents an important target for antimicrobial stewardship efforts. A prospective study could determine the optimal antibiotic selection for those with complicated appendicitis.

ABBREVIATIONS

aOR: adjusted odds ratio
CI: confidence interval
LOS: length of stay
PHIS: Pediatric Health Information System

Accepted for publication Apr 28, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Seattle Children's Research Institute Center for Clinical and Translational Research Clinical Research Scholars Program to Dr Kronman.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2016;138;

DOI: 10.1542/peds.2015-4547 originally published online June 28, 2016;

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