Annals of Surgery Publish Ahead of Print
DOI:10.1097/SLA.0000000000005747

Association between antibiotic redosing prior to incision and risk of incisional site infection in children with appendicitis

1. Shannon L. Cramm, MD, MPH (Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA)*
1. Nicole M. Chandler, MD (Division of Pediatric Surgery, Johns Hopkins All Children's Hospital, St. Petersburg, FL)*
2. Dionne A. Graham, PhD (Program for Patient Safety and Quality, Boston Children's Hospital, Boston, MA)
3. Shaun M. Kunisaki, MD, MSc (Division of General Pediatric Surgery, Johns Hopkins Children's Center, Johns Hopkins School of Medicine, Baltimore, MD)
4. Robert T. Russell, MD, MPH (Department of Surgery, Division of Pediatric Surgery, University of Alabama at Birmingham, Children's of Alabama, Birmingham, AL)
5. Martin L. Blakely, MD, MS (Department of Pediatric Surgery, Vanderbilt Children's Hospital, Vanderbilt University Medical Center, Nashville, TN)
6. Aaron M. Lipskar, MD (Division of Pediatric Surgery, Cohen Children's Medical Center, Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY)
7. Myron Allukian, MD (Division of Pediatric, General, Thoracic, and Fetal Surgery, Children's Hospital of Philadelphia, Philadelphia, PA)
8. Danielle I. Aronowitz, MD (Division of Pediatric, General, Thoracic, and Fetal Surgery, Children's Hospital of Philadelphia, Philadelphia, PA)
9. Brendan T. Campbell, MD, MPH, FACS (Department of Surgery, Connecticut Children's Hospital, Hartford, CT)
10. Devon T. Collins, MPH, CPH, CHES (Department of Surgery, Children's National Hospital, Washington, D.C.)
11. Sarah J. Commander, MD, MHS (Department of Surgery, Duke Children's Hospital and Health Center, Duke University School of Medicine, Durham, NC)
12. Robert A. Cowles, MD (Division of Pediatric Surgery, Yale New Haven Children's Hospital and Yale School of Medicine, New Haven, CT)
13. Jennifer R. DeFazio, MD (Division of Pediatric Surgery, New York Presbyterian Morgan Stanley Children's Hospital, Columbia University Vagelos Colleges of Physicians and Surgeons, New York, NY)
14. Joseph R. Esparaz, MD, MPH (Department of Surgery, Division of Pediatric Surgery, University of Alabama at Birmingham, Children's of Alabama, Birmingham, AL)
15. Christina Feng, MD (Department of Surgery, Children's National Hospital, Washington, D.C.)
16. Cornelia L. Griggs, MD (Division of Pediatric Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA)
17. Richard A. Guyer, MD, PhD (Division of Pediatric Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA)

18. David N. Hanna, MD (Department of Surgery, Vanderbilt Children's Hospital, Vanderbilt University Medical Center, Nashville, TN)
19. Anastasia M. Kahan, MD (Division of Pediatric Surgery, New York Presbyterian Morgan Stanley Children's Hospital, Columbia University Vagelos Colleges of Physicians and Surgeons, New York, NY and Department of Surgery, Mount Sinai Health System, New York, NY)
20. Olivia A. Keane, MD (Division of Pediatric Surgery, Department of Surgery, Children's Healthcare of Atlanta, Emory University, Atlanta, GA)
21. Abdulraouf Lamoshi, MD, MPH, MS (Division of Pediatric Surgery, Cohen Children's Medical Center, Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY)
22. Carla M. Lopez, MD (Division of General Pediatric Surgery, Johns Hopkins Children's Center, Johns Hopkins School of Medicine, Baltimore, MD)
23. Elizabeth Pace, MD (Division of Pediatric Surgery, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA)
24. Maia D. Regan, BS (Department of Surgery, Connecticut Children's Hospital, Hartford, CT)
25. Matthew T. Santore, MD (Division of Pediatric Surgery, Department of Surgery, Children's Healthcare of Atlanta, Emory University, Atlanta, GA)
26. Stefan Scholz, MD, PhD, FACS, FAAP (Division of Pediatric Surgery, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA)
27. Elisabeth T. Tracy, MD (Department of Surgery, Duke Children's Hospital and Health Center, Duke University School of Medicine, Durham, NC)
28. Sacha A. Williams, MD, MS, MPH (Division of Pediatric Surgery, Johns Hopkins All Children's Hospital, St. Petersburg, FL)
29. Lucy Zhang, MD (Division of Pediatric Surgery, Yale New Haven Children's Hospital and Yale School of Medicine, New Haven, CT)
30. Shawn J. Rangel, MD, MSCE (Dept. of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA)

On behalf of the Eastern Pediatric Surgery Network

*co-first authors

Corresponding Author:

Shawn J. Rangel, MD, MSCE
Department of Surgery
Boston Children's Hospital
Harvard Medical School

300 Longwood Avenue, Fegan-3
Boston, MA 02115

Tel: 617-355-3040
Fax: 617-730-0298

Email: shawn.rangel@childrens.harvard.edu

Funding: This work was funded through the Children's Hospital Surgery Foundation.

Running head: Pre-incision antibiotics in appendicitis (37/40 characters)

Authorship contributions:

This was a multicenter study involving 16 centers, requiring data acquisition from all sites as well as input on center-level practices and differences to both design the study as well as interpret data. Please see below for full list of authors' contributions.

All Authors gave final approval of the manuscript version to be published.

Shannon Cramm
1. Made substantial contributions to analysis design, to analysis, and interpretation of data
2. Made substantial contributions to manuscript draft

Nicole Chandler
1. Made substantial contributions to analysis design, acquisition of data, and interpretation of data
2. Made substantial contributions to manuscript draft

Dionne Graham
1. Made substantial contributions to analysis design, analysis, and interpretation of data
2. Critically revised manuscript

Shaun Kunisaki, Robert Russell, Martin Blakely, Aaron Lipskar, Myron Allukian
1. Made substantial contributions to conception, to acquisition of data and to interpretation of data
2. Critically revised manuscript

Danielle Aronowitz, Brendan Campbell, Devon Collins, Sarah Commander, Robert Cowles, Jennifer DeFazio, Joseph Esparaz, Christina Feng, Cornelia Griggs, Richard Guyer, David Hanna, Anastasia Kahan, Olivia Keane, Abdulraouf Lamoshi, Carla Lopez, Elizabeth Pace, Maia Regan, Matthew Santore, Stefan Scholz, Elisabeth Tracy, Sacha Williams, Lucy Zhang
1. Made substantial contributions to acquisition of data and interpretation of data
2. Critically revised manuscript

Shawn Rangel
1. Made substantial contributions to analysis conception and design, to analysis, and to interpretation of data
2. Made substantial contributions to manuscript draft

Keywords
Pediatric appendicitis, incisional surgical site infection, antimicrobial stewardship, antibiotics, surgical antimicrobial prophylaxis

Association between antibiotic redosing prior to incision and risk of incisional site infection in children with appendicitis

Structured Abstract

Objective: To evaluate whether redosing antibiotics within an hour of incision is associated with a reduction in incisional surgical site infection (iSSI) in children with appendicitis.

Summary of background data: Existing data remain conflicting as to whether children with appendicitis receiving antibiotics at diagnosis benefit from antibiotic redosing prior to incision.

Methods: This was a multicenter retrospective cohort study using data from the Pediatric National Surgical Quality Improvement Program augmented with antibiotic utilization and operative report data obtained though supplemental chart review. Children undergoing appendectomy at 14 hospitals participating in the Eastern Pediatric Surgery Network from 7/2016-6/2020 who received antibiotics upon diagnosis of appendicitis between 1-6 hours prior to incision were included. Multivariable logistic regression was used to compare odds of iSSI in those who were and were not redosed with antibiotics within one hour of incision, adjusting for patient demographics, disease severity, antibiotic agents, and hospital-level clustering of events.

Results: 3,533 children from 14 hospitals were included. Overall, 46.5% were redosed (hospital range: 1.8%-94.4%, $p<0.001$) and iSSI rates were similar between groups (redosed: 1.2% vs. non-redosed: 1.3%; OR 0.84, [95%CI 0.39-1.83]). In subgroup analyses, redosing was associated with lower iSSI rates when cefoxitin was used as the initial antibiotic (redosed: 1.0% vs. non-redosed: 2.5%; OR 0.38, [95%CI 0.17-0.84]), but no benefit was found with other antibiotic regimens, longer periods between initial antibiotic administration and incision, or with increased disease severity.

Conclusions: Redosing of antibiotics within one hour of incision in children who received their initial dose within 6 hours of incision was not associated with reduction in risk of incisional site infection unless cefoxitin was used as the initial antibiotic.

Introduction

Acute appendicitis is the most common abdominal surgical emergency in childhood, accounting for the greatest relative burden of surgical site infections (SSI) in pediatric surgery.[1-4] Management of appendicitis is also associated with the greatest number of cumulative antibiotic treatment days of all surgical conditions in childhood.[5] Efforts to define optimal antibiotic management for children with appendicitis therefore have important public health implications in balancing the goals of SSI prevention and antimicrobial stewardship.

Children with appendicitis often receive antibiotics at time of diagnosis to halt disease progression.[4] Additional administration of antibiotics within an hour of incision is theorized to reduce incisional SSI risk by optimizing antibiotic tissue levels at the time of operation and is currently recommended by multidisciplinary guidelines.[6-11] However, these guidelines were developed for elective procedures in patients not already receiving antibiotics for established or suspected infections. Existing data in children with appendicitis are both limited and conflicting as to whether those who receive initial antibiotics more than an hour before incision benefit from additional antibiotic redosing within an hour of incision to reduce risk of incisional SSI.[12-14] Prevention of incisional SSI is an important goal given the increased morbidity, length of stay, and resource utilization associated with infectious complications in pediatric appendicitis.[2,15-18] Conversely, unnecessary overutilization of antibiotics has been associated with increased risk of antibiotic-associated adverse events (e.g., Clostridium difficile infection and acute renal injury) and antimicrobial resistance.[11,19,20]

With the considerations above, the goal of this multicenter comparative effectiveness analysis was to evaluate whether antibiotic redosing within an hour of incision is associated with lower rates of incisional SSIs in children with appendicitis who received initial antibiotic treatment upon diagnosis. We further sought to explore this relationship in the context of different antibiotic regimens and timelines of antibiotic administration which could plausibly impact both tissue concentration at time of incision and SSI risk. By leveraging data from a large number of hospitals across different geographic regions, we aimed to increase the applicability of the study results to a wide variety of patient populations and practice scenarios.

Methods

Data Source

This was a retrospective, multicenter cohort study utilizing demographic, clinical, and outcomes data from the American College of Surgeon's National Surgical Quality Improvement Program-Pediatric (NSQIP-Pediatric) augmented with operative report and antibiotic utilization data obtained through supplemental chart review. The NSQIP-Pediatric database includes a wide array of disease-specific, clinical data for the purpose of comparing risk-adjusted adverse event and resource utilization data among its 152 member hospitals.[21] Data are collected through a rigorous chart review process by dedicated surgical clinical reviewers using standardized criteria and definitions. Accuracy of NSQIP-Pediatric data is facilitated through periodic auditing, mandatory recertification for data abstractors, and availability of American College of Surgeons clinical support to address questions regarding definitions and data abstraction protocol.[22]

Supplemental chart review was performed at each study site to collect full operative report data to assess disease severity and perioperative antibiotic utilization data for each patient identified from the NSQIP-Pediatric database. To facilitate a standardized chart review process across all participating centers, a manual of operations and standardized training videos for data collection were reviewed by all sites. 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 any study data.

This study was approved by the institutional review board of Boston Children's Hospital (IRB-P00039633), which serves as the data coordinating center maintaining the Eastern Pediatric Surgery Network (EPSN) appendicitis database.

Study Cohort

The study cohort included children (≤18 years of age) undergoing appendectomy for acute appendicitis (uncomplicated and complicated) identified from the NSQIP-Pediatric database at 14 hospitals participating in the EPSN research consortium from July 1, 2015 to June 30, 2020. Children were considered for inclusion if they received a single dose of antibiotics within one and six hours prior to incision. This time interval was chosen based on the intent of the analysis to explore whether there is benefit to redosing antibiotics earlier than manufacturer recommendations for the most commonly used antibiotics in the management of pediatric appendicitis (cefoxitin, ceftriaxone combined with metronidazole, and piperacillin-

tazobactam).[7,23-25] A secondary analysis was conducted in children who were initially treated with ceftriaxone combined with metronidazole with an extended pre-incision window from 6 hours to 24 hours to assess the utility of redosing in the context of once-daily dosing regimen of ceftriaxone combined with metronidazole.[26,27] Exclusion criteria included initial administration of antibiotics without full colorectal coverage and missing antibiotic utilization data (timing or agent).

Classification of Exposures and Outcomes

The primary exposure was redosing of antibiotics within one hour of incision. The primary outcome of the study included 30-day postoperative incisional SSI as defined by NSQIP-Pediatric criteria.[28]

Statistical Analysis

Chi square test and Wilcoxon rank sum tests were used for univariate comparisons. The Pearson correlation coefficient (r) was used to examine the hospital-level relationship between redosing rate and incisional SSI outcomes. Multivariable mixed effects logistic regression was used to compare the odds of incisional SSI in patients who were and were not redosed at the patient-level, adjusting for sex, race/ethnicity, insurance type (public, private, other), disease severity, initial antibiotic agents administered at time of diagnosis, and clustering of outcomes within study centers. Disease severity was assigned from review of operative reports and categorized into three strata based on previously validated NSQIP-Pediatric criteria: no intraoperative

findings of complicated disease (uncomplicated), one intraoperative finding of complicated disease, and multiple intraoperative findings of complicated disease.[28,29]

Additional models were utilized to explore potential effect modification of the association between redosing and incisional SSI outcomes based on factors plausibly related to tissue concentration and SSI risk. These included models to explore the influence of time between initial antibiotic administration and incision (categorized into quartiles), initial antibiotic regimen based on most commonly utilized agents (cefoxitin, ceftriaxone combined with metronidazole, piperacillin-tazobactam), spectrum of coverage associated with redosing agents (full or partial colorectal coverage), and severity of disease (uncomplicated versus complicated).

Measures of association were reported as adjusted odds ratios (OR). Analyses were performed with SAS statistical software (version 9.4; SAS Institute, Inc). Statistical significance threshold was considered with a two-sided $P<0.05$.

Results

After applying exclusion criteria, 3533 children who underwent appendectomy for uncomplicated and complicated appendicitis at 14 children's hospitals who received initial antibiotics within 1-6 hours prior to incision were included in the primary analysis (Figure 1). The median number of patients per site was 226.5 (IQR 123.5-386.5). In the final cohort, 79.6% were diagnosed with uncomplicated appendicitis, 39.7% were female, and 32.9% were publicly insured. Patient demographics, apart from sex, varied by redosing group. Patients in the redosed

group were more likely to be White (redosed: 38.6%, non-redosed: 29.0%, p<0.01) and have uncomplicated appendicitis (redosed: 81.2%, non-redosed: 78.3%, p=0.01).

Antibiotic utilization and redosing patterns

Of the 3533 children included, 1642 (46.5%) were redosed within an hour of incision. Redosing rates varied 52-fold across hospitals, ranging from 1.8% to 94.4% (Figure 2). The median time between initial antibiotic administration and incision was 3.1 hours (IQR 2.0-4.5) and was longer in children who were redosed compared to those who were not (3.8 hours [IQR 2.6-5.0] vs. 2.6 hours [IQR 1.7-3.8]; p<0.01).

There were 43 unique approaches to preoperative antibiotic management when considering antibiotic agents used and redosing practices, with the ten most common approaches accounting for 91% of all cases (Table 1). The most common antibiotic treatment approach in children who were redosed was cefoxitin administered both as the initial antibiotic upon diagnosis and for redosing, accounting for 47.0% of all redosed patients. The most common antibiotic treatment approach in patients who were not redosed was ceftriaxone combined with metronidazole given at time of diagnosis, accounting for 52.1% of non-redosed patients.

Incisional Surgical Site Infection Rates and Redosing

The overall incisional SSI rate was 1.2% and unadjusted rates were similar in patients who were and were not redosed (redosed: 1.2%, non-redosed: 1.3%, p=0.88). Rates of incisional SSI

ranged from 0.0% to 3.7% across hospitals (Figure 2). No correlation was found at the hospital-level between redosing rate and incisional SSI rate (r=-0.31, p=0.28; Figure 2). Median time from initial antibiotic administration to incision in patients who developed an incisional SSI was similar in patients who were and were not redosed (redosed: 2.8 hours, non-redosed: 2.9 hours, p=0.90).

In multivariable analysis adjusting for patient characteristics, disease severity, initial antibiotic agent, and center-level clustering, redosing was not associated with a reduction in the odds of incisional SSI (OR 0.84, 95% CI 0.39-1.83; p=0.66; Figure 3). In supplemental models examining potential effect modification, there remained no association between redosing and incisional SSI across different initial antibiotic to incision time quartiles, categories of appendicitis severity, and antimicrobial spectrum of redosing agents (Figure 3). When the analysis allowed for effect modification by initial antibiotics administered at time of diagnosis, redosing was associated with a 62% reduction in odds of incisional SSI for children initially receiving cefoxitin (OR 0.38, 95% CI 0.17-0.84, p=0.02; Figure 3), while no benefit was found in those treated initially with ceftriaxone combined with metronidazole or piperacillin-tazobactam (Figure 3). In a supplemental analysis limited to children treated with ceftriaxone and metronidazole only with an extended pre-incision redosing window to 24 hours (Figure 1), incisional

SSI rates were similar between patients who were and were not redosed overall and across each quartile of time between initial antibiotic administration and incision on univariate analysis (Table 2). Multivariable modeling was not possible for this 24-hour pre-incision ceftriaxone combined with metronidazole cohort due to low event rates.

Discussion

In this multicenter analysis of 3533 children with appendicitis, no benefit was seen with antibiotic redosing within an hour of incision in the majority of children who received their initial dose of antibiotics upon diagnosis. With the exception of patients initially treated with cefoxitin, lack of benefit remained even when stratifying the analysis by initial antibiotic regimen, antimicrobial spectrum of coverage of redosing agents, increasing interval between initial antibiotic administration and incision, and severity of disease. Furthermore, no benefit was found for redosing in children treated receiving a single dose of ceftriaxone combined with metronidazole up to 24 hours prior to appendectomy, an increasingly popular management strategy in this cohort of children. The results of this study also demonstrated considerable equipoise among hospitals in both the rate of and approach to redosing in children with appendicitis.

Existing data from single-center experiences are conflicting as to whether redosing within an hour of incision reduces SSI risk. In a retrospective, single-center analysis of 697 children with uncomplicated appendicitis, administration of antibiotics within an hour of incision was associated with a 78% reduction in odds of any SSI compared to those who received antibiotics more than an hour prior to incision.[13] In a retrospective, single-center analysis of 478 children with appendicitis, no difference in incisional SSI rates were found in patients who received their final preoperative dose of antibiotics before or within an hour of incision (2.0 vs. 2.1%).[14] In another retrospective, single-center analysis of 1549 children with acute appendicitis, similar rates of SSI were also found in children receiving antibiotics prior to or within an hour of

incision (uncomplicated appendicitis: SSI 2.1% versus 3.0%; complicated appendicitis: SSI 19.6% versus 18.5%).[12] Conflicting results from these studies may reflect variation among hospitals' redosing practices, differences in definitions used for both exposures and outcomes, and limited generalizability of single-center experiences to the broader scope of pediatric surgical practice.

To our knowledge, this study represents the largest and first multicenter comparative effectiveness analysis exploring the utility of antibiotic redosing in children with appendicitis. The primary analysis was limited to children who had initially received antibiotics within one and six hours prior to incision in order to address the clinically pertinent question of whether redosing earlier than manufacturer recommended guidelines is necessary to optimize SSI prevention. A secondary analysis of children treated with ceftriaxone combined with metronidazole was expanded to up to 24 hours prior to incision to evaluate the benefit of redosing in children treated with once-daily dosing.[26,27] The time limits on this study design were intended to address the limitations of existing data in that no previous studies have examined the utility of redosing on SSI outcomes in children receiving their initial antibiotics treatment diagnosis. The generalizability of the present study is strengthened by the inclusion of data from 14 children's hospitals, representing a wide range of antibiotic treatment approaches, clinical practice environments, and patient populations. The large, multicenter sample allowed for the exploration of the relationship between redosing and SSI risk in the context of different antibiotics agents, timelines of administration between initial administration and incision, and disease severity, all which could plausibly influence tissue-level antibiotic concentration at incision and SSI risk.

The findings of this study call into question the utility of routinely redosing within an hour of incision for surgical prophylaxis in children with appendicitis. Rates of incisional SSI were exceedingly low overall, and no statistically or clinically meaningful differences in outcomes were found between redosed and non-redosed patients. The potential benefit of avoiding potentially unnecessary antibiotic utilization at both the patient and population level cannot be overstated. Use of perioperative antibiotic prophylaxis has been associated with increased risk of Clostridium difficile infection, acute renal injury, and allergic reaction including anaphylaxis in several large, multicenter cohort studies.[11,19,20] At the population level, prolongation of antibiotic treatment has been identified as a major driver of antimicrobial resistance.[30-32] When considering that nearly half of children with appendicitis in this study were redosed, these data highlight a considerable opportunity to reduce antibiotic utilization and improve antibiotic stewardship in the management of this condition.

It is noteworthy that a benefit with redosing prior to manufacturer's recommended guidelines was found in patients treated initially with cefoxitin. It is important to emphasize that pharmacokinetic considerations around dosing interval may be very different between infection treatment and prevention, with antibiotic half-life, minimal inhibitory concentration (MIC), and physiologic characteristics (e.g., intraoperative blood loss and renal failure) playing important roles. The recommended dosing interval for cefoxitin based on half-life and MIC for treatment of established infections is 6 hours, while that for intraoperative redosing to maintain adequate tissue concentration is 2 hours.[7] The results of this study suggest that pre-incision cefoxitin redosing should potentially follow intraoperative dosing guidelines rather than those for infection

treatment. From the perspective of clinical practice and practicality, the requirement of redosing to optimize incisional site infection prevention in this cohort may add to the mounting evidence suggesting cefoxitin may not be an ideal antibiotic treatment for children with appendicitis.[24] Furthermore, cefoxitin is not recommended for treatment of complicated appendicitis by the Surgical Infection Society or consensus guidelines endorsed by the American Society of Hospital Pharmacists and Infectious Disease Society of America.[7,33] Differentiating complicated from uncomplicated appendicitis in the preoperative setting can be challenging, and a change from cefoxitin to a more broad-spectrum regimen after complicated disease is recognized intraoperatively may result in treatment delay and potentially higher risk of surgical site infection.[34-36]

The results of this study must be interpreted in the context of its limitations. Although NSQIP-Pediatric utilizes a rigorous chart review process and standardized definitions for both exposures and outcomes, data collected in NSQIP-Pediatric are retrospective and errors in misclassification and identification of outcomes are possible. Hospitals participating in the EPSN research consortium are largely academic children's hospitals which could potentially limit the generalizability of these data to other clinical settings. Despite the large number of patients included in this study, the analysis was underpowered to detect the small absolute differences in incisional SSI rates given the very low event rates observed between groups. However, undetected differences which may be statistically significant (e.g., type II error) may not reflect clinically meaningful ones given that the adjusted absolute risk difference of incisional SSIs between groups was only 0.2%. This would translate into a number needed to treat estimate of 500 patients to prevent a single incisional SSI. Whether or not this difference in incisional SSI

rates is wide enough to justify the excess cost and potential harm of roughly 500 additional antibiotic doses will need to be considered by individual surgeons. Finally, multiple comparisons used in this analysis to explore a broad range of potential effect modifications may also increase the likelihood of type I error. This may have been evidenced by higher rates of organ space SSI found with redosing for some subgroup analyses of antibiotic-to-incision time quartiles despite the implausibility of higher rates being associated with more intensive antibiotic treatment. Although this may reflect residual confounding despite adjustment for patient characteristics and center-level clustering, it is noteworthy that higher rates of redosing were found with less severe disease, suggesting that residual confounding due to severity was unlikely.

Despite the limitations above, the results of this analysis call into question the utility of antibiotic redosing within an hour of incision in the majority of children with appendicitis who receive initial antibiotics upon diagnosis. With the exception of children initially treated with cefoxitin, these data would argue that the routine practice of redosing prior to that recommended by manufacturer guidelines may have limited ability to further reduce incisional SSIs in a clinically meaningful manner. When considering the magnitude of equipoise in redosing practices identified in this study, abandonment of routine redosing could significantly reduce antibiotic utilization burden and improve antimicrobial stewardship in the management of pediatric appendicitis.

Acknowledgements

The authors would like to acknowledge the Children's Hospital Surgery Foundation for their financial support.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol.* 1990;132(5):910-925.
2. Cameron DB, Graham DA, Milliren CE, et al. Quantifying the Burden of Interhospital Cost Variation in Pediatric Surgery: Implications for the Prioritization of Comparative Effectiveness Research. *JAMA Pediatr.* 2017;171(2):e163926.
3. Cameron DB, Serres SK, Glass CC, et al. Leveraging the Incidence, Burden, and Fiscal Implications of Unplanned Hospital Revisits for the Prioritization of Prevention Efforts in Pediatric Surgery. *Ann Surg.* 2020;271(1):191-199.
4. He K, Rangel SJ. Advances in the Diagnosis and Management of Appendicitis in Children. *Adv Surg.* 2021;55:9-33.
5. Kronman MP, Hersh AL, Gerber JS, et al. Identifying Antimicrobial Stewardship Targets for Pediatric Surgical Patients. *J Pediatric Infect Dis Soc.* 2015;4(4):e100-108.
6. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg.* 2017;152(8):784-791.
7. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70(3):195-283.
8. Ban KA, Minei JP, Laronga C, et al. Executive Summary of the American College of Surgeons/Surgical Infection Society Surgical Site Infection Guidelines-2016 Update. *Surg Infect (Larchmt).* 2017;18(4):379-382.
9. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med.* 1992;326(5):281-286.
10. Bucher BT, Warner BW, Dillon PA. Antibiotic prophylaxis and the prevention of surgical site infection. *Curr Opin Pediatr.* 2011;23(3):334-338.
11. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of Duration and Type of Surgical Prophylaxis With Antimicrobial-Associated Adverse Events. *JAMA Surg.* 2019;154(7):590-598.
12. Somers KK, Eastwood D, Liu Y, Arca MJ. Splitting hairs and challenging guidelines: Defining the role of perioperative antibiotics in pediatric appendicitis patients. *J Pediatr Surg.* 2020;55(3):406-413.
13. Mueck KM, Putnam LR, Anderson KT, Lally KP, Tsao K, Kao LS. Does compliance with antibiotic prophylaxis in pediatric simple appendicitis matter? *J Surg Res.* 2017;216:1-8.
14. Litz CN, Asuncion JB, Danielson PD, Chandler NM. Timing of antimicrobial prophylaxis and infectious complications in pediatric patients undergoing appendectomy. *J Pediatr Surg.* 2018;53(3):449-451.
15. Rice-Townsend S, Barnes JN, Hall M, Baxter JL, Rangel SJ. Variation in practice and resource utilization associated with the diagnosis and management of appendicitis at freestanding children's hospitals: implications for value-based comparative analysis. *Ann Surg.* 2014;259(6):1228-1234.
16. Rice-Townsend S, Hall M, Barnes JN, Baxter JK, Rangel SJ. Hospital readmission after management of appendicitis at freestanding children's hospitals: contemporary trends and financial implications. *J Pediatr Surg.* 2012;47(6):1170-1176.

17. Anandalwar SP, Cameron DB, Graham DA, et al. Association of Intraoperative Findings With Outcomes and Resource Use in Children With Complicated Appendicitis. *JAMA Surg.* 2018;153(11):1021-1027.
18. Farach SM, Danielson PD, Walford NE, Harmel RP, Jr., Chandler NM. Operative Findings Are a Better Predictor of Resource Utilization in Pediatric Appendicitis. *J Pediatr Surg.* 2015;50(9):1574-1578.
19. Rangel SJ, Fung M, Graham DA, Ma L, Nelson CP, Sandora TJ. Recent trends in the use of antibiotic prophylaxis in pediatric surgery. *J Pediatr Surg.* 2011;46(2):366-371.
20. Sandora TJ, Fung M, Melvin P, Graham DA, Rangel SJ. National Variability and Appropriateness of Surgical Antibiotic Prophylaxis in US Children's Hospitals. *JAMA Pediatr.* 2016;170(6):570-576.
21. Bruny JL, Hall BL, Barnhart DC, et al. American College of Surgeons National Surgical Quality Improvement Program Pediatric: a beta phase report. *J Pediatr Surg.* 2013;48(1):74-80.
22. American College of Surgeons National Surgical Quality Improvement Program Pediatric Operations Manual: Appendectomy. In:July 1, 2021.
23. Cameron DB, Melvin P, Graham DA, et al. Extended Versus Narrow-spectrum Antibiotics in the Management of Uncomplicated Appendicitis in Children: A Propensity-matched Comparative Effectiveness Study. *Ann Surg.* 2018;268(1):186-192.
24. Kashtan MA, Graham DA, Melvin P, et al. Ceftriaxone Combined With Metronidazole is Superior to Cefoxitin Alone in the Management of Uncomplicated Appendicitis in Children: Results from a Multicenter Collaborative Comparative Effectiveness Study. *Ann Surg.* 2021;274(6):e995-e1000.
25. Kashtan MA, Graham DA, Melvin P, Hills-Dunlap JL, Anandalwar SP, Rangel SJ. Ceftriaxone with metronidazole versus piperacillin/tazobactam in the management of complicated appendicitis in children: Results from a multicenter pediatric NSQIP analysis. *J Pediatr Surg.* 2021.
26. St Peter SD, Tsao K, Spilde TL, et al. Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial. *J Pediatr Surg.* 2008;43(6):981-985.
27. Hurst AL, Olson D, Somme S, et al. Once-Daily Ceftriaxone Plus Metronidazole Versus Ertapenem and/or Cefoxitin for Pediatric Appendicitis. *J Pediatric Infect Dis Soc.* 2017;6(1):57-64.
28. National Surgical Quality Improvement Program-Pediatric Appendectomy Procedure Targeted Semi-Annual Report. *Released by the American College of Surgeons.* 2020.
29. Cameron DB, Anandalwar SP, Graham DA, et al. Development and Implications of an Evidence-based and Public Health-relevant Definition of Complicated Appendicitis in Children. *Ann Surg.* 2020;271(5):962-968.
30. Paschke AA, Zaoutis T, Conway PH, Xie D, Keren R. Previous antimicrobial exposure is associated with drug-resistant urinary tract infections in children. *Pediatrics.* 2010;125(4):664-672.
31. Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet.* 2016;387(10014):176-187.
32. Antibiotic resistance threats in the United States. *US Centers for Disease Control and Prevention.* 2013.

33. Nadler EP, Gaines BA, Therapeutic Agents Committee of the Surgical Infection S. The Surgical Infection Society guidelines on antimicrobial therapy for children with appendicitis. *Surg Infect (Larchmt).* 2008;9(1):75-83.
34. Leeuwenburgh MM, Wiezer MJ, Wiarda BM, et al. Accuracy of MRI compared with ultrasound imaging and selective use of CT to discriminate simple from perforated appendicitis. *Br J Surg.* 2014;101(1):e147-155.
35. Obinwa O, Peirce C, Cassidy M, Fahey T, Flynn J. A model predicting perforation and complications in paediatric appendicectomy. *Int J Colorectal Dis.* 2015;30(4):559-565.
36. Church JT, Coughlin MA, Antunez AG, Smith EA, Bruch SW. Creating diagnostic criteria for perforated appendicitis using cross-sectional imaging. *Pediatr Surg Int.* 2017;33(9):1007-1012.

Table 1. Variation in antibiotic treatment approaches prior to incision and associated incisional surgical site infection (SSI) rates in children with appendicitis at 14 children's hospitals.

				Incisional SSI	
Initial Antibiotic Agent	**Redosing Agent**	**N**	**%**	**N**	**%**
Ceftriaxone/Metronidazole	None given	986	27.9%	11	1.1%
Cefoxitin	Cefoxitin	771	21.8%	6	0.8%
Piperacillin-tazobactam	None given	598	16.9%	7	1.2%
Piperacillin-tazobactam	Piperacillin-tazobactam	347	9.8%	7	2.0%
Cefoxitin	None given	158	4.5%	4	2.5%
Ampicillin-sulbactam	Ampicillin-sulbactam	107	3.0%	0	0.0%
Ceftriaxone/Metronidazole	Cefazolin	94	2.7%	1	1.1%
Ciprofloxacin/Metronidazole	None given	52	1.5%	1	1.9%
Ampicillin-sulbactam	None given	51	1.4%	0	0.0%
Cefoxitin	Cefazolin	49	1.4%	1	2.0%
Ceftriaxone/Metronidazole	Cefoxitin	49	1.4%	0	0.0%
Other initial regimen (not redosed)	None given	46	1.3%	1	2.2%
Other initial regimen (redosed)	Other redosed regimen	225	6.4%	5	2.2%

Table 2. Association between antibiotic redosing within an hour of incision and incisional surgical site infection in children receiving a single dose of ceftriaxone combined with metronidazole upon diagnosis within 24 hours of appendectomy.

	All Patients (N=2149)		**Redosed (N=536)**		**Not Redosed (N=1613)**		
Incisional Site Infections	**N**	**%**	**N**	**%**	**N**	**%**	**P-Value**
By Antibiotic-to-Incision Time Quartile							
1.0-2.8 hours (N=552)	4	0.7%	0	0.0%	4	0.8%	0.51
2.9-5.4 hours (N=528)	7	1.3%	1	0.9%	6	1.4%	0.54
5.5-9.1 hours (N=534)	3	0.6%	0	0.0%	3	0.8%	0.22
9.2-24 hours (N=535)	3	0.6%	0	0.0%	3	0.9%	0.19
Overall	17	0.8%	1	0.2%	16	1.0%	0.07

Figure 1. Assembly of the primary and supplemental study cohorts.

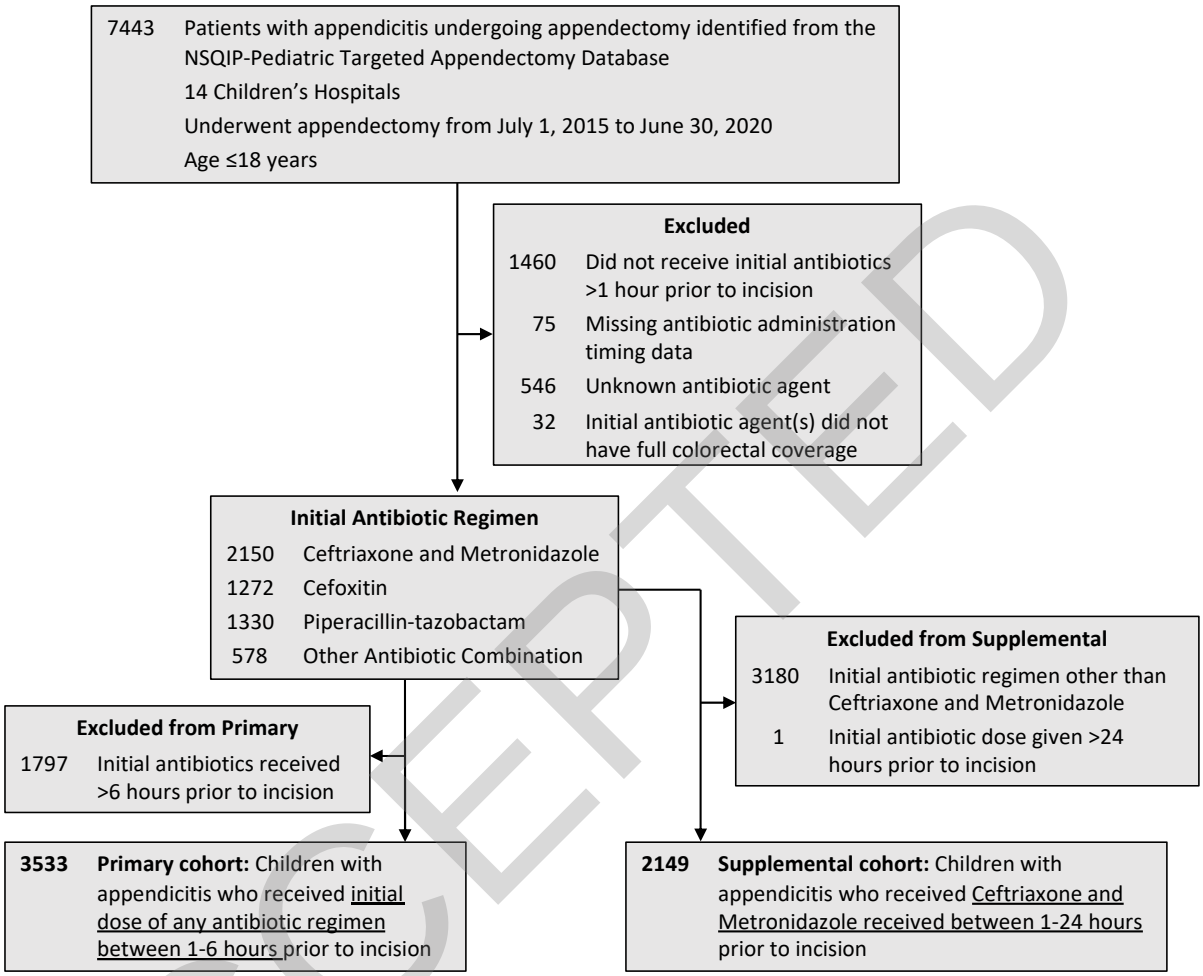


Figure 2. Variation in rates of antibiotic redosing within an hour of incision and surgical site infection (SSI) rates in children with appendicitis at 14 children's hospitals. Correlation between antibiotic redosing and incisional SSI measures were calculated using the Pearson correlation.

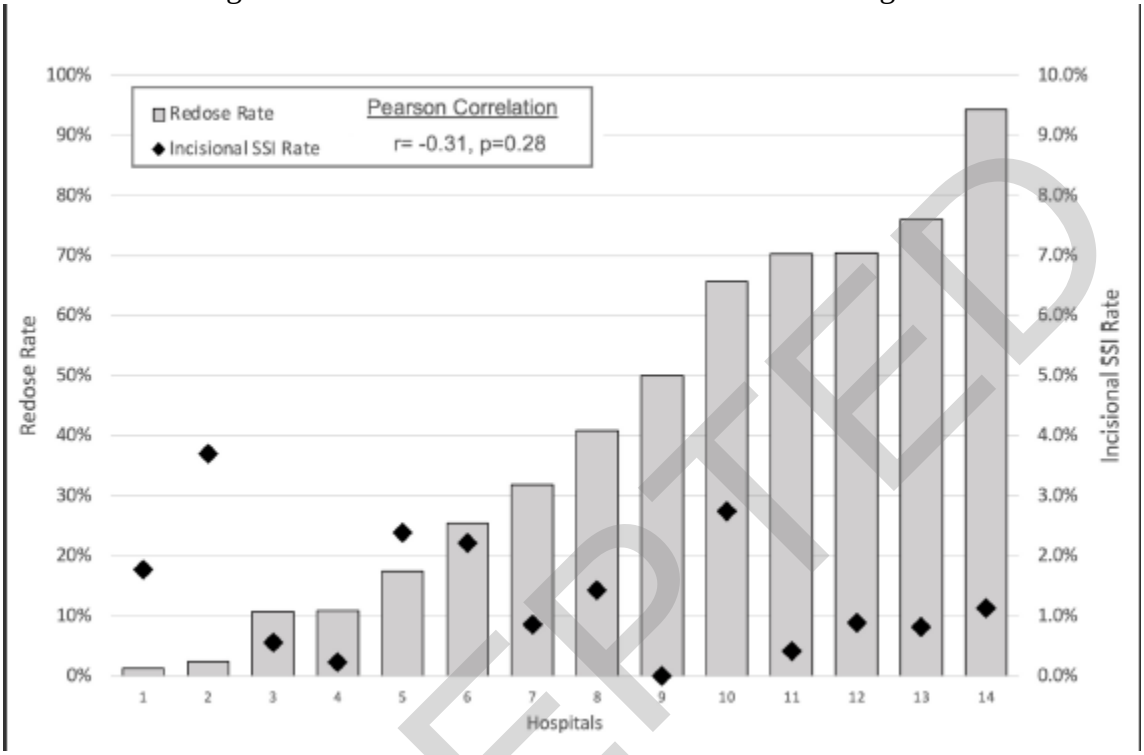
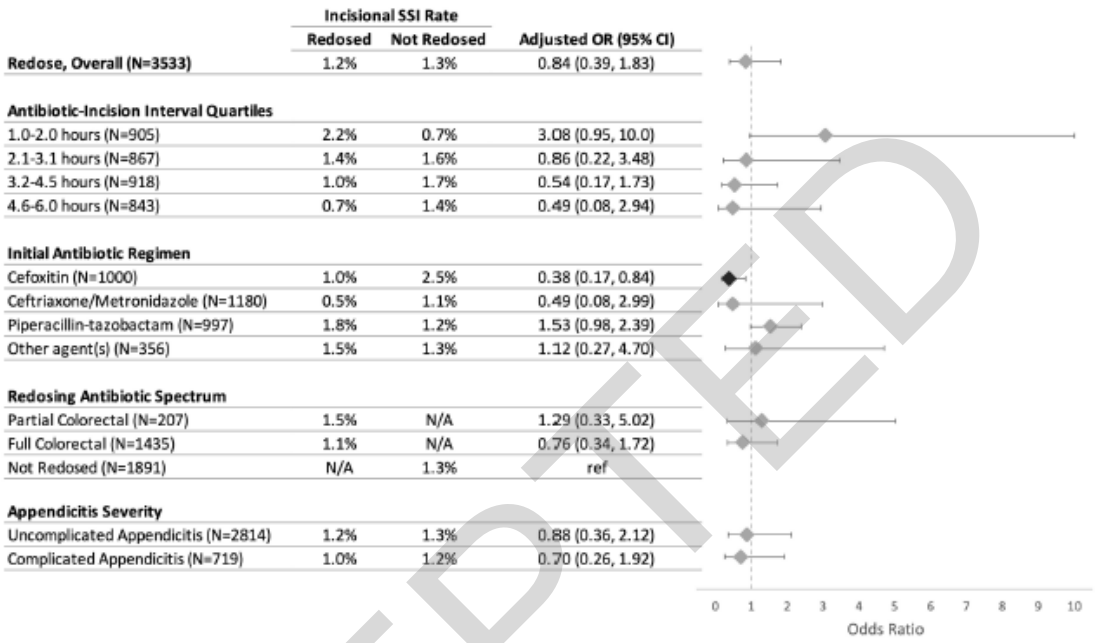


Figure 3. Association between antibiotic redosing within an hour of incision and incisional surgical site infection (SSI) in children with appendicitis at 14 children's hospitals who received their initial antibiotic dose between one and six hours prior to incision.



	Incisional SSI Rate		
	Redosed	Not Redosed	Adjusted OR (95% CI)
Redose, Overall (N=3533)	1.2%	1.3%	0.84 (0.39, 1.83)
Antibiotic-Incision Interval Quartiles			
1.0-2.0 hours (N=905)	2.2%	0.7%	3.08 (0.95, 10.0)
2.1-3.1 hours (N=867)	1.4%	1.6%	0.86 (0.22, 3.48)
3.2-4.5 hours (N=918)	1.0%	1.7%	0.54 (0.17, 1.73)
4.6-6.0 hours (N=843)	0.7%	1.4%	0.49 (0.08, 2.94)
Initial Antibiotic Regimen			
Cefoxitin (N=1000)	1.0%	2.5%	0.38 (0.17, 0.84)
Ceftriaxone/Metronidazole (N=1180)	0.5%	1.1%	0.49 (0.08, 2.99)
Piperacillin-tazobactam (N=997)	1.8%	1.2%	1.53 (0.98, 2.39)
Other agent(s) (N=356)	1.5%	1.3%	1.12 (0.27, 4.70)
Redosing Antibiotic Spectrum			
Partial Colorectal (N=207)	1.5%	N/A	1.29 (0.33, 5.02)
Full Colorectal (N=1435)	1.1%	N/A	0.76 (0.34, 1.72)
Not Redosed (N=1891)	N/A	1.3%	ref
Appendicitis Severity			
Uncomplicated Appendicitis (N=2814)	1.2%	1.3%	0.88 (0.36, 2.12)
Complicated Appendicitis (N=719)	1.0%	1.2%	0.70 (0.26, 1.92)