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Adverse events associated with surgical antibiotic prophylaxis for outpatient circumcisions at US children's hospitals

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Summary

Introduction
Doctors often use surgical antibiotic prophylaxis (SAP) despite limited evidence to support its efficacy. We sought to determine the association between SAP in children undergoing circumcision and the rate of perioperative adverse events.

Material and methods
We performed a retrospective study of males >30 days old and <18 years old who underwent circumcision from 2004 to 2014 using the Pediatric Health Information System database. We excluded inpatients and those with any concomitant procedures. We used chi-square or Fisher's exact test to determine the association between SAP and allergic reaction and any of the following within 30 days: penile reoperation, hospital visit, or surgical site infection (SSI). We performed mixed effects logistic regression controlling for age, race, insurance, and clustering of similar practice patterns by hospital.

Results
84,226 patients were included: median age 2.2 years; 61.0% public insurance, 39.6% white. 8944 (10.6%) received SAP. On bivariate analysis, there were no associations between SAP and SSI (0.1% vs. 0.2%, $p = 0.5$), penile reoperation (0.01% vs. 0.04%, $p = 0.4$), or hospital visit (5.5% vs. 5.5%, $p = 0.8$). Patients who received SAP were more likely to have a perioperative allergic reaction than those who did not (3.5% vs. 2.9%, $p = 0.0004$). On multivariate analysis, those who received SAP had 1.5 times the odds of an allergic reaction (OR 1.5, 95% CI 1.3–1.7; $p < 0.0001$) and a hospital visit (OR 1.2, 95% CI 1.1–1.3; $p = 0.0021$) compared with those who did not (Table).

Discussion
SAP did not decrease the risk of penile reoperation or SSI. Use of SAP was associated with an increased risk of allergic reactions and hospital visits. Strengths of the study include its large sample size, which enabled detection of rare outcomes with adequate statistical power and the generalizability of our findings to many patients and other types of procedures. Limitations include the lack of outpatient data and the possibility that we could have overestimated the incidence of allergic reactions by including patients who received epinephrine for some other reason.

Conclusions
We found no compelling evidence to support the use of SAP in children undergoing circumcision and it was associated with an increased risk of allergic reaction and hospital visits. This study highlights the need for specialty-specific guidelines for pediatric urologic procedures regarding the use of antibiotics for prophylaxis and for vigilant monitoring of practice variation.

Table Bivariate and multivariate mixed effects logistic regression examining the association between SAP and perioperative allergic reaction, penile reoperation, SSI, and ED visit or readmission.

Outcome	SAP unadjusted OR (p-value)	SAP adjusted OR (p-value)
Perioperative allergic reaction	1.2 (95% CI 1.2–1.6; $p < 0.0001$)	1.5 (95% CI 1.3–1.7; $p < 0.0001$)
Penile reoperation	0.29 (95% CI 0.04–2.13; $p = 0.2231$)	n/a
SSI	0.8 (95% CI 0.4–1.5; $p = 0.4880$)	n/a
ED visit or readmission	1.1 (95% CI 1.0–1.2; $p = 0.0392$)	1.2 (95% CI 1.1–1.3; $p = 0.0021$)

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Introduction

Postoperative surgical site infections (SSIs) are a source of potentially preventable perioperative morbidity. Doctors often prescribe surgical antibiotic prophylaxis (SAP) in clean urologic procedures despite minimal evidence that it decreases the risk of SSI in selected procedures such as nephrectomy or nephroureterectomy [1,2]. There is even less evidence to support the use of SAP for pediatric urologic procedures, particularly those with a "clean" wound classification [3–5]. There are also concerns about potential adverse events associated with SAP in children and adults undergoing urologic procedures leading to uncertainty about its risk/benefit ratio [6,7]. Rangel and colleagues examined trends in the use of SAP for pediatric surgical procedures from 2005 to 2009 using the Pediatric Health Information System (PHIS) database and found that adverse events were significantly more likely in children who received SAP than in those who did not [7]. SAP patients had increased odds of *C. difficile* infection (OR 4.1) and of receiving epinephrine (OR 1.8), a surrogate event for an allergic reaction [7]. In a similar study using PHIS data from 2010 to 2013, Sandora and colleagues also found that children who received SAP had a higher rate of *C. difficile* infection (OR 3.3) and of epinephrine administration (OR 2.0) [8]. In a retrospective, population-based analysis by Macy et al., the most common, serious cephalosporin-associated adverse drug reactions were *C. difficile* infection within 90 days (0.91%), nephropathy within 30 days (0.15%), and all-cause death within 1 day (0.10%) [9]. Antibiotic exposure in the first year of life has also been linked to the development of childhood allergic diseases including atopic dermatitis, asthma, and allergic rhinitis in a recent birth cohort study [10].

Routine antibiotic use may also contribute to hypersensitivity drug reactions, antibiotic resistance, and increased healthcare costs. β-lactam antibiotics are the most common cause of hypersensitivity drug reactions mediated by specific immunological mechanisms [11]. Early studies reported a prevalence of allergic reactions to penicillin ranging from 0.7% to 10% of the population, with anaphylaxis occurring in 0.015% to 0.004% of the cases [12]. Cephalosporins, one of the most commonly used classes of anti-bacterial agents for SAP in urology, have an approximately 10% cross-reactivity with β-lactam antibiotics [13,14]. This has important implications for children who may be exposed to antibiotics for the first time during a surgical procedure.

Furthermore, there is evidence that antibiotic prophylaxis may be associated with the development of resistant bacteria. In a 5-year, prospective survey of children admitted for urinary tract infections (UTI), Giardino *et al.* reported an increase in the rate of gram-negative UTIs (from 2.69 episodes/1000 hospital days to 4.54 episodes/1000 hospital days) and an associated increase in infections caused by extended spectrum β-lactamase producing strains [15]. They also noted that the administration of long-term, low-dose antibiotics for prophylaxis is a common practice in their unit. Finally, there is evidence that implementation of evidence-based care process models and antibiotic stewardship programs decrease antibiotic duration, reduce antibiotic prescribing and shorten hospital stays [16,17].

We chose to evaluate the effects of SAP on patients undergoing circumcision, as it is one of the most commonly performed pediatric procedures in the USA [18]. We hypothesized that children who received SAP would have an increased risk of allergic reactions, but no difference in the rate of surgical site infections (SSI) or readmissions compared with those who did not receive SAP. The purpose of this study was to determine the association between SAP in children undergoing circumcision and the rate of perioperative adverse events and SSI.

Materials and methods

Data source

PHIS is an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation encounter-level data from over 45 not-for-profit, tertiary care pediatric hospitals in the USA. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (e.g. pharmaceuticals, imaging, and laboratory) into PHIS. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study we included data from 43 children's hospitals.

Study population

We performed a retrospective cohort study of all males between 30 days and 18 years of age who underwent a circumcision or circumcision revision (ICD-9-CM procedure code 64.0) in an ambulatory or observation setting from January 2004 to December 2014. We included patients admitted for observation, to avoiding missing patients whose status changed from ambulatory to observation because of an intraoperative adverse event (e.g. allergic reaction). (In the PHIS database, patients are classified based on their status at the time of discharge.) We excluded inpatients and those who had length of stay >2 days. We excluded cases where multiple procedures were performed at the same time to ensure that the use of SAP was associated with circumcision or circumcision revision. We also excluded hospitals that did not report separate charges for antibiotics administered in the operating room and those that did not contribute ambulatory surgery billing data. SAP was defined as a charge for an oral, intravenous, or intramuscular antibiotic on the date of circumcision.