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Cefazolin versus Alternative Antibiotics for Surgical Prophylaxis in Children With a Reported Penicillin Allergy

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ABSTRACT

Introduction: Cefazolin is the antibiotic of choice for prevention of surgical site infections for many pediatric surgical procedures. In patients with a reported penicillin allergy, cefazolin is often replaced with vancomycin or clindamycin. Outcomes may be worse when alternatives are used.

Materials and methods: We performed a retrospective review among children (aged 0–18 y) who underwent surgical procedures (orthopedic, cardiac, neurosurgical, or plastic surgery) where cefazolin was indicated for surgical prophylaxis to determine the risk of developing a new drug allergy when cefazolin was administered preoperatively compared to vancomycin or clindamycin. Allergies occurring after the preincision antibiotic dose was given and up to 7 d after surgery were included.

Results: A total of 46,418 patients were included; 89.6% received cefazolin. Seven (0.02%) patients had an adverse reaction to cefazolin; none had a prior history of penicillin allergy. Compared to cefazolin, adverse reactions were 7 times more likely (95% confidence interval 2–22.3) with clindamycin and 56.8 times more likely (95% confidence interval 16.3–181.7) with vancomycin.

Conclusions: Cefazolin drug reactions in children are rare, while reactions to alternatives are more common. We suggest cefazolin should be administered to all children preoperatively, when indicated, regardless of allergy unless the allergy is to cefazolin itself.

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Introduction

Cefazolin is the antibiotic of choice for prevention of surgical site infections for many pediatric surgical procedures due to its

favorable safety profile, low cost, and activity against microorganisms of concern.¹ In 2018, we began recommending cefazolin for surgical prophylaxis when indicated among all patients at our pediatric hospital, including those with a reported penicillin

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(PCN) allergy. This change was made because cross reactivity between cephalosporins and PCN is not thought to be related to the beta-lactam ring itself, but rather influenced by similarities in R1 side chains. Cefazolin does not share any R1 side chains with any current Food and Drug Administration-approved beta-lactam.² Therefore, the presumed risk of an adverse reaction to cefazolin among patients with a reported PCN allergy is expected to be no different than the general population (1%-3%).^{3,4}

In patients with a reported PCN allergy, cefazolin is often replaced with a non-beta-lactam antibiotic. Vancomycin and clindamycin are frequently selected as alternatives. However, outcomes may be worse when alternatives to cefazolin are used as surgical prophylaxis, including increased risk of surgical site infections, resistance, cost, hospital length of stay, and mortality.⁵⁻⁸ Given the increase in utilization of cefazolin at our institution among all patients for surgical prophylaxis, even those with a reported PCN allergy, we sought to determine the risk of developing a new drug allergy to cefazolin compared to alternatives. We anticipated reactions to cefazolin would occur at the same rate among patients with or without a reported PCN allergy.

Methods

This was a single site, retrospective cohort quality improvement evaluation among children (aged 0-18 y) who underwent surgical procedures (orthopedic, cardiac, neurosurgical, or plastic surgery), where cefazolin was indicated for surgical prophylaxis from January 1, 2013, to December 31, 2022. This date range was selected to include all patients retrospective to the implementation of our most recent electronic health record. We collected demographic information (e.g., date of birth, sex, race/ethnicity), surgical procedure, preoperative allergies, preoperative antibiotic received as well as outcome data, which included development of new drug allergy to the given antibiotic. A preoperative antibiotic allergy was included when the allergy was added to the electronic medical record before the anesthesia start date and time. A new postoperative allergy was included when it was added to the electronic allergy record any time after the preincision antibiotic dose was recorded as given and up to 7 d after surgery. Among patients with a recorded postoperative allergy, the documentation within the electronic health record was reviewed (TZ) and used to determine severity. "PCN" allergies were inclusive of all PCN derivatives (e.g., PCN, ampicillin, and amoxicillin) and combined. "Cephalosporin" allergies were collected and displayed by specific agent. Our primary outcome was to identify the rate of new cefazolin allergy (regardless of allergy history) compared to alternative antibiotics (vancomycin or clindamycin).

Demographic and other patient characteristics were compared among the patient groups using chi-square or Fisher's exact tests. Continuous/numeric variables, such as time to new allergy, were compared using Mann-Whitney tests. Nonparametric tests were used due to skewed distribution of the variables. Statistical analysis was performed using the R statistical system (R Foundation for Statistical Computing, Vienna, Austria). Odds ratios were computed using the R epitools procedure.

This project was reviewed by our local Human Research Protection Program and was deemed a quality improvement project that does not require Investigational Review Board review and approval. There were no interventions or interactions with human subjects. All analyzed data were deidentified.

Results

Among 46,418 pediatric surgical patients, 89.6% (41,578 patients) received cefazolin and the remainder (10.4%) received either clindamycin or vancomycin (Table 1). Of those that received cefazolin, 4.1% had a prior PCN allergy and 0.5% had a prior cephalosporin allergy. Seven patients (0.02%) had an adverse reaction to perioperative cefazolin (Table 2), but none of these patients had a prior history of PCN allergy. One of the seven had a prior cefdinir allergy. Five reactions were considered grade 1, two were grade 2, and none were grade 3-5, based on the United States Drug Allergy Registry grading scale.⁹ Compared to cefazolin, children were 7 times more likely (95% CI 2-22.3) to experience an adverse drug reaction to clindamycin and 56.8 times more likely (95% CI 16.3-181.7) for vancomycin. The power to detect a significant difference ($P < 0.05$) given the observed sample sizes and proportions of adverse drug reactions was 97.9%.

Discussion

Our evaluation of over 40,000 children locally who received cefazolin for preoperative prophylaxis supports that cefazolin is safe to administer in children. Adverse reactions were rare, and when present, reactions were mild to moderate in nature. This was true even among children with a reported PCN allergy. Approximately 8% of the children we reviewed reported a preoperative PCN allergy, which is consistent with a prevalence of 9.4% globally and 9% in the United States.^{3,10}

Among patients with a preoperative PCN allergy, nearly half received cefazolin. This is consistent with a change in practice at our institution during the evaluation period where our Antimicrobial Stewardship team provided education to pharmacists, surgeons, and anesthesiologists that cefazolin is safe to administer among patients with a reported PCN allergy. We also suppressed PCN-cephalosporin cross-reactivity alerts, unless the reaction was anaphylaxis, for which we recommended the provider consider risk versus benefits. The proportion of patients receiving cefazolin despite a PCN allergy (and even with a cephalosporin allergy) in our evaluation is similar to those in adult patients when alerts were suppressed for non-immunoglobulin E-mediated PCN allergies.¹¹⁻¹³

We anticipated that adverse reactions to cefazolin would occur at the same rate among patients with and without a reported preoperative PCN allergy. This was indeed the case, though our absolute number of reactions to cefazolin was low (7 out of 41,578 patients). It is possible we missed events if reactions were not documented. Of the 7, none had a previously reported PCN allergy (1 had a previous cefdinir allergy). All reactions were minor, responding to antihistamines or

Table 1 – Characteristics of study population, by antibiotic received.

Variable	Cefazolin	Clindamycin or vancomycin	P value
N (%)	41,578 (89.6)	4840 (10.4)	
Age (y), median (IQ)	7 (1,13)	9 (3,14)	<0.001
Sex, N (%)			0.002 (excl. indeterminate)
Male	23,335 (56.1)	2604 (53.8)	
Female	18,242 (43.9)	2236 (46.2)	
Indeterminate	1 (0)		
Race/ethnicity, N (%)			<0.001
White/Caucasian	25,497 (61.3)	3050 (63)	
Black/African American	6571 (15.8)	846 (17.5)	
Hispanic/Latinx	5513 (13.3)	577 (11.9)	
Asian	1425 (3.4)	104 (2.1)	
Other	284 (0.7)	40 (0.8)	
Two or more races	1164 (2.8)	104 (2.1)	
Refused/unknown	1124 (2.7)	119 (2.5)	
Penicillin allergy (presurgery), N (%)	1701 (4.1)	2138 (44.2)	<0.001
Cephalosporin allergy (presurgery), N (%)	204 (0.5)		
(n= 4 had >1 cephalosporin allergy)			
Cefdinir	140		
Cephalexin	30		
Ceftriaxone	12		
Cefepime	8		
Cefprozil	4		
Cefotaxime	2		
Cefaclor	1		
Cefadroxil	1		
Cefazolin	1		
Cefixime	1		
Ceftazidime	1		
Cefuroxime	1		
Cephalosporin, not identified	6		

IQR = interquartile.

discontinuation of cefazolin administration. All patients remained hemodynamically stable and none required an escalation of care (e.g., respiratory or inotropic support). For two patients, the intraoperative notes questioned if the reaction was due to the cefazolin or other drugs administered within close proximity (i.e., paralytics, anesthetics). The safety

of cefazolin among adults with a PCN allergy has previously been reported, though similar safety data in children is lacking. Sirkeoja et al.¹⁴ evaluated 1395 adult patients with a PCN allergy label who received cefazolin as preoperative prophylaxis. None of these exhibited a reaction to cefazolin. Murphy et al.¹⁵ evaluated the occurrence of cefazolin perioperative

Table 2 – Acquisition of new allergy, by antibiotic received.

Variable	Cefazolin	Clindamycin	Vancomycin	OR (95% CI) or P value
N (%)	41,578 (89.6)	4308 (9.3)	532 (1.1)	
Adverse drug reaction, N (%)	7 (0.02)*	5 (0.1)	5 (0.9)	Clindamycin versus cefazolin: 7 (2–22.3) Vancomycin versus cefazolin: 56.8 (16.3–181.7)
Time (hours) from surgery to new allergy, median (IQR)	18.3 (6.7,32)	19.0 (1.8,99.6)	11.9 (1.0–12.4)	0.47

* All 7 occurred in patients without a previously reported penicillin allergy; 1 had a prior cefdinir allergy. None of the reactions were severe. CI = confidence interval; IQR = interquartile range; OR = odds ratio.

anaphylaxis in adult patients and found a low overall rate of anaphylaxis (0.02%). They found no difference between patients with and without a PCN allergy label. Others have reported similar findings. The safety previously demonstrated in adults, the overall low (and minor) adverse reaction rate in our evaluation, and the increased rate of drug reactions when given an alternative (clindamycin or vancomycin) reinforce the recommendation to prescribe cefazolin to all patients (even those with a PCN allergy) when it is the indicated drug for surgical prophylaxis.

Conclusions

We observed the use of perioperative cefazolin among children at our institution was the safest approach when indicated, regardless of reported PCN allergy status. This project builds upon the increasing data in adults that cefazolin is safe to administer if the patient does not have a specific cefazolin allergy. We suggest cefazolin should be administered to all children preoperatively, when cefazolin is indicated as first line, regardless of PCN allergy status and even among patients with a cephalosporin allergy, if the allergy is not to cefazolin itself.

Disclosure

None declared.

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None.

CRediT authorship contribution statement

Tracy Zembles: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Cheryl Singer:** Writing – review & editing, Validation, Data curation. **Evelyn Kuhn:** Writing – review & editing, Formal analysis, Data curation. **Caroline Frahm:** Writing – review & editing, Visualization, Methodology. **Richard Berens:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Michael McCormick:** Writing – review & editing, Visualization, Methodology. **Michelle Mitchell:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis.

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