



Penicillin allergy and surgical prophylaxis: Cephalosporin cross-reactivity risk in a pediatric tertiary care center ☆☆☆★★★

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ABSTRACT

Background: First generation cephalosporins are commonly used as antibiotic prophylaxis prior to surgery. Patients labeled as penicillin-allergic are often precluded from receiving cephalosporins because of an allergic cross-reactivity. The aims of this study were to evaluate the clinical practice for surgical prophylaxis at Nationwide Children's Hospital and to determine the incidence of adverse effects and allergic reactions when using cephalosporins in patients labeled as penicillin-allergic.

Methods: A retrospective chart review was performed to identify patients who were allergic to penicillin, penicillin antibiotic family, who required surgical treatment for an existing medical condition, and received an antibiotic to prevent surgical site infection.

Results: Five hundred thirteen penicillin-allergic patients were identified, encompassing 624 surgical cases. Cephalosporins were administered in 153 cases (24.5%) with cefazolin used 83% of the time. Only one documented case of nonanaphylactic reaction was reported. Clindamycin was the most common cephalosporin substitute ($n = 387$), and the reported adverse reaction rate was 1.5%. No cases of anaphylaxis were documented.

Conclusions: Our data suggest that the administration of cephalosporins for surgical prophylaxis following induction of anesthesia in a patient with a known or reported penicillin-allergy appears appropriate and results in a lower adverse event rate that when clindamycin is administered.

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The administration of perioperative antibiotics is an important strategy to reduce the risk of surgical site infections. Prophylaxis with a cephalosporin is often recommended. Antibiotics used in the perioperative period are typically credited with up to 15% of all anaphylactic reactions. Most antibiotic-related reactions are associated with

penicillin and/or cephalosporins [1]. The literature suggests that the incidence of cross-reactions between penicillin and cephalosporins is approximately 10%. However, Campagna et al. [2] postulated that the actual cross-reactivity might be as low 1%.

The highest risk of cross-reactivity appears to be related to the utilization of first generation cephalosporins in patients labeled penicillin-allergic. Although third and fourth generation cephalosporins appear to carry a very low cross-reactivity risk, they are not routinely used for the purpose of prevention of wound site infections [3]. DePestel et al. [4] analyzed the evidence of cross-reactivity between penicillin and cephalosporin antibiotics, and after reviewing 44 studies, concluded that physicians could safely prescribe cephalosporins to patients with non-life threatening penicillin reactions. Hameed and Robinson [5] provided additional information by conducting a database search, including cases describing the administration of cephalosporins to patients with positive penicillin skin tests or documented anaphylaxis, with an emphasis on reported anaphylactic reactions in children. They concluded that there were no reported published cases of anaphylaxis from cephalosporin use in children with reported anaphylaxis to penicillin. However, many anesthesia providers remain reluctant to administer cephalosporins to patients with previously suspected or documented penicillin allergy. In such cases, alternative antibiotics including

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vancomycin or clindamycin are administered as preoperative antibiotic prophylaxis. Although effective, these antibiotics present a higher anesthesia adverse effect profile than cephalosporins including the potential for adverse hemodynamic and cardiac side effects [6,7]. Additionally, the indiscriminate use of vancomycin may be one mechanism responsible for the emergence of resistant organisms [8].

The purpose of the present study was aimed at examining our practice for the use of perioperative antibiotics at Nationwide Children's Hospital (Columbus, Ohio), focusing on presurgical antibiotic prophylaxis in patients with a registered penicillin-allergy. The incidence of adverse effects and the type of allergic reactions when using cephalosporins were determined. A secondary aim was to determine the most commonly prescribed alternative non-cephalosporin antibiotics and the incidence and type of allergic reactions with these agents. Another secondary aim was to determine the timeliness of antibiotic delivery for presurgical prophylaxis by determining its administration relative to time of incision. Our final secondary objective was to determine if a specific age group was at greater risk of allergic reactions based on incidence of presentation.

1. Methods

After approval by the institutional review board, IRB11-00822, requirements for informed consent were waived due to the retrospective observational nature of the study. A retrospective charts review of patients requiring intraoperative administration of antibiotics for surgical prophylaxis was conducted for the years 2010–2012. This study was registered with the United States National Institutes of Health under identification number: NCT02036840. Inclusion criteria included patients who had a registered penicillin allergy, or penicillin antibiotic family related allergy, required surgical treatment and received antibiotic prophylaxis as part of their anesthetic care. The focus was to analyze data related to patients who received cephalosporin antibiotics intraoperatively, as well as alternative antibiotics for the same indication.

Data acquisition used the Epic patient chart system (Epic Headquarters, Wisconsin, USA) used at Nationwide Children's Hospital Enterprise Data Warehouse. Antibiotic generics and commercial names consisted of: penicillin, penicillins, penicillin G, penicillin V, ampicillin, ampicillin/sulbactam, amoxicillin/clavulanate, nafcillin, piperacillin, piperacillin/tazobactam, and ticarcillin. Patients registered as allergic to the aforementioned antibiotics who underwent surgical treatment were retained. This list was cross-matched using a second set of keywords to screen for patients who received antibiotics intraoperatively. Many surgical procedures do not require intraoperative antibiotics, or have an established pre-surgical antibiotic strategy, e.g., vancomycin for elective ventriculoperitoneal shunts, or piperacillin/ticarcillin for patients scheduled for appendectomy. The second keyword search included the words: amoxicillin, ampicillin, cefazolin, cefoxitin, ceftazidime, ciprofloxacin, clindamycin, gentamicin, metronidazole, vancomycin, zosyn. The resulting list was created and data stored using Apex software (Oracle Corporation, Redwood Shores, CA, USA).

A subset of patients with perioperative reported allergic reaction was identified. Using the electronic record via Picis Anesthesia Manager (Picis Incorporated, Wakefield MA, USA), a screening tool was created to identify patients with documented intraoperative allergic symptoms using a keyword set for search criteria that consisted of "hives", "skin rash", "fever", "erythema", "arrhythmia", and "anaphylaxis". Patients identified with the above-mentioned clinical signs consequent to allergic reactions were further screened for blood pressure changes >30% above or below preoperative values. Perioperative documentation of allergies was limited to documented allergies in Anesthesia Manager, encompassing documented anesthesia time in preoperative surgical area, intraoperative care, and up to time of discharge from postanesthesia care unit. Exclusion criteria included patients with primary cephalosporin allergy.

Data processing and analysis was executed using QlikView software (Qlik Tech, Lund, Sweden) enabling statistical analysis. Statistical analysis was performed by obtaining percentages based on total number of

cases per variable observed as depicted in different tables. For average values obtained per measured variable, a standard deviation was calculated. Nonparametric and/or contingency table analyses were used to determine the significance of the observed information. A $P < 0.05$ was accepted as statistically significant.

2. Results

A total of 1428 patients were identified as penicillin or penicillin family allergic, requiring procedural or surgical intervention in the operating room, accounting for 1963 surgical cases. From this initial group, only patients who received perioperative antibiotic prophylaxis were included in the final cohort, accounting for 513 patients or 624 distinct surgical interventions. There were two hundred sixty-three males and 250 females. Fifty patients were aged 0–5 years, 75 were 6–10 years, and 388 were ≥ 11 years of age. The mean age was 15 ± 7.9 years. The youngest patient requiring antibiotics intraoperatively was 5 months old. One hundred forty patients received cephalosporins intraoperatively in the course of 153 surgical cases, as there were patients who made more than one trip to the operating room. The most commonly reported allergic reactions to penicillins are listed in Table 1. Some patients had more than one documented type of allergic reaction to a previously exposed antibiotic. Of the entire cohort of patients labeled as penicillin-allergic, a cephalosporin was administered in 153 cases (24.5%).

Cefazolin was the most commonly used cephalosporin, administered in 127 surgical interventions. Cefoxitin was administered in the remaining 26 cases. In the cephalosporin group, one patient had a documented reaction to cefazolin with the development of hives and erythema (0.6%). This patient was treated successfully with intravenous diphenhydramine. In 16 cases, patients received cephalosporins two or more times intraoperatively without consequences. There were 11 cases in which a cephalosporin was administered in combination with another antibiotic without reported reactions. No documented cases of anaphylactic reactions were noted (Fig. 1).

Of the remaining 375 patients with penicillin-allergy, totaling 471 cases, various antibiotics were administered for surgical prophylaxis (Table 2). The most commonly administered antibiotic agent in this group was clindamycin, accounting for 387 cases, followed by gentamicin (75 cases), vancomycin (30 cases), ciprofloxacin (19 cases), piperacillin/ticarcillin (Zosyn™) (11 cases), metronidazole (5 cases), ampicillin (2 cases), and amoxicillin (1 case). In the clindamycin group, 8 patients were identified to have documented allergic reactions. Six patients were reported to have a rash, 2 developed urticaria, and one developed erythema. In 60 cases, clindamycin was administered in combination with another antibiotic without adverse effects reported. In all, 2% of patients who received clindamycin had a reported reaction. There were no documented cases of anaphylaxis. There were no documented allergic or adverse responses to gentamicin or vancomycin. In the ciprofloxacin group, 3 patients developed allergic responses. One patient experienced hives, another had a skin rash, and the third patient developed systemic hypotension that was directly associated to antibiotic administration. In the entire cohort, 3 of 19 patients who received ciprofloxacin developed allergic manifestations for an incidence of approximately 15%.

We attempted to look at antibiotic administration time relative to incision for purposes of analyzing our practice compliance with institutional presurgical prophylaxis guidelines. We found 476 cases received their first dose of antibiotics before skin incision, during the time of induction of anesthesia, at an average time of 15 ± 17 minutes prior

Table 1
Reported allergic reactions to penicillin by parents or patients.

Antibiotic	Skin rash	Hives	Unknown	Anaphylaxis
Penicillin/penicillin antibiotic family	40% (n = 207)	27% (n = 142)	18% (n = 92)	4% (n = 21)



Fig. 1. EMR: electronic medical record; PICIS: preoperative anesthesia record; Anesthesia manager: intraoperative/postoperative anesthesia record; APEX: data storage software; Qlikview: data processing/statistical software.

to incision. This accounted for 76% of all cases. In 90 cases (14%), the antibiotic was administered after skin incision at an average of 12 ± 18 minutes. For the remaining patients (9%), the time of administration of the antibiotic in regard to skin incision time was not recorded, as these cases lacked a defined incision time. In this situation, most procedures were classified as cardiac catheterization or cystoscopy.

Lastly, we aimed to determine if a particular population subset was at greater risk of incidence of allergic reactions. We proceeded by classifying our cohort into 4 different age groups. The first group was the 0–5 years of age totaling 58 cases. In this subset, no reactions were found after antibiotic administration. The second group included patients ranging from 6 to 10 years of age. This group included 86

Table 3

Reported reactions based on patient age and type of reaction.

Age (years)	Case count	Number of reactions	Rash	Hives	Erythema	Anaphylaxis	Hemodynamic instability
0–5	58	0	0	0	0	0	0
6–10	86	0	0	0	0	0	0
11–18	334	12	7	4	2	0	1
>18	146	0	0	0	0	0	0

cases and no reactions were noted. The third group included 11 to 18 year olds ($n = 334$ cases). There were 12 reactions noted. The last group was for patients older than 18 years of age. A total of 146 patients were included without reported reactions (Table 3).

3. Discussion

Antibiotic surgical prophylaxis is one of several important strategies to prevent postoperative surgical site infections. This therapy is recommended for a wide variety of interventions, and first generation cephalosporins remain the cornerstone [9]. Problems arise when patients scheduled for surgery have documented or reported allergy to penicillin antibiotics.

Antibiotic anaphylactic reactions are reported to account for up to 15% of all anaphylactic reactions in the perioperative setting [1]. Cephalosporins had been traditionally credited for cross-reactivity with penicillin on the order of 10% [3], but a 2011 comprehensive review concluded that overall cross reactivity between penicillins and cephalosporins was approximately 1% when using first generation cephalosporins. Our present study showed a cross-reactivity of 0.6% when using first generation cephalosporins in the perioperative setting, thus correlating well with previously reported pediatric data.

In 2002 an exhaustive search of the literature failed to demonstrate any cases of anaphylaxis from cephalosporin administration in patients with documented penicillin allergy [5]. However, a case of intraoperative anaphylaxis to cefuroxime in a patient chronically receiving penicillin v prophylaxis was published separately later that year [10]. In the present study it was not possible to find a single case of anaphylaxis following cephalosporin administration in the operating room over a three-year review thus highlighting how rare this event can be.

Ahmed et al. [11] retrospectively evaluated antibiotic use in a total of 173 patients with penicillin-allergy. Twenty-one patients (12%) tested positive to a penicillin skin test while 152 patients (88%) tested negative. Only one patient with a negative penicillin skin test (0.7%) had an adverse drug reaction (eye swelling) to cephalexin, and none of the patients with a positive skin test who received a cephalosporin had an adverse drug reaction. Ahmed's reported incidence of 0.6% supports our findings; however, many of his patients received oral instead of intravenous antibiotics. Here our study is different in that all reported data come from pediatric patients who received intravenously dosed antibiotics, illustrating the current anesthesia experience in the operating room rather than extrapolating results from other clinical settings.

In the present study, the most frequent reaction reported following the administration of an antibiotic was skin rash accounting for 40%, whereas hives was second at 27%. The clinical difficulty in using rash and hives as signs for predicting allergic reactions is their nonspecificity to IgE-mediated type I reactions, particularly in the absence of reported or documented pruritus. The IgE mediated reactions would include pruritic rash, angioedema, or bronchospasm. Pichichero [12] reported that the use of a cephalosporin for penicillin-allergic patients is safe when the allergic reaction is not IgE mediated. Nevertheless, many anesthesia providers refrain from using cephalosporins in the setting of documented penicillin allergy due to concerns of potentially triggering an allergic reaction, a concept that cannot be substantiated in view of the present study and previously reported conclusions. Our study

Table 2

Other antibiotics administered to penicillin-allergic patients.

Antibiotic	Number of cases	Number of reported reactions
Cefazolin	127	1
Cefoxitin	26	0
Clindamycin	387	8
Gentamicin	75	0
Vancomycin	30	0
Ciprofloxacin	19	3
Piperacillin/Ticarcillin	11	0
Metronidazole	5	0
Ampicillin	2	0
Amoxicillin	1	0

showed a parallel to that conservative anesthesia practice as cephalosporins were only administered to approximately one quarter of all patients who had a documented penicillin-allergy, but debunked this medical myth by demonstrating the low incidence of allergic reactions. It additionally highlighted that allergic phenomena is more common with alternative antibiotics. These findings emphasize the need to consider altering the current paradigm in clinical practice. Lastly, our results showed that the majority of reported allergic reactions curiously occurred in older kids, particularly in children older than 11 years of age. These results were supported by Macy and Poon's [13] report in which increasing age was one of three primary factors involved in greater incidence of allergic reactions.

This study was limited by its retrospective nature, which may have affected the accuracy of data recorded. However, because of the nature of the problem we can be sure that the most important allergic reaction (anaphylaxis) would not have been missed on the electronic chart record. Review of electronic records allowed us to clearly identify all patients who received medications that would have been used to treat allergic reactions including diphenhydramine, corticosteroids, or epinephrine. It is possible that clinical signs and symptoms of an allergic reaction could have been inappropriately attributed to the administration of antibiotics when in fact they were due to some other medication or condition. However, considering the incidence of allergic reactions was low, it is safe to suggest that the risk of cross-allergic reaction is still very small.

In conclusion, the administration of a cephalosporin to a patient with a history of penicillin allergy is a safe therapeutic strategy for surgical wound prophylaxis, and remains clinically recommended. The incidence of allergic problems was noted to be higher with alternative antibiotics. However, this recommendation does not hold for patients with reported anaphylactic reactions, positive skin test to penicillins, or those with documented severe reactions such as Stevens–Johnson syndrome. In such instances, alternative medications are recommended. When cephalosporins are administered for those patients, we would recommend the administration of a test dose (5%–10% of the dose) and the slow administration of the remainder of the cephalosporin over a 5–10 minute period, rather than the rapid intravenous infusion commonly used in anesthesia practice. When alternative antibiotics are administered, prolonged infusion times of 30–60 minutes are generally recommended for clindamycin and ciprofloxacin. Infusion times of 60–120 minutes are

recommended for vancomycin. The prolonged infusion times may make the preincision administration of antibiotics more problematic.

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