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Concise Communication

Variability of surgical prophylaxis in penicillin-allergic children

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Abstract

We retrospectively evaluated the effect of penicillin adverse drug reaction (ADR) labeling on surgical antibiotic prophylaxis. Cefazolin was administered in 86% of penicillin ADR-negative (−) and 28% penicillin ADR-positive (+) cases. Broad-spectrum antibiotic use was more common in ADR(+) cases and was more commonly associated with perioperative adverse drug events.

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Approximately 10% of patients have a documented penicillin allergy, although the incidence of a true allergic reaction is much less frequent.[1] A penicillin adverse drug reaction (ADR) label is associated with the unnecessary use of broad-spectrum antibiotics, prolonged hospitalization, increased prevalence of multidrug-resistant infections, and increased risk of death compared to those without a penicillin ADR label.[2–4] ADRs may refer to allergic reactions (eg, rash or anaphylaxis) or side effects (eg, diarrhea). Unfortunately, clinicians often fail to obtain a thorough ADR history or to clarify the type of reported reaction prior to prescribing medication.[2,3]

Antibiotic prophylaxis is utilized routinely to reduce the risk of surgical site infections (SSIs) in high-risk pediatric procedures.[5,6] Cefazolin is the drug of choice for many procedures because it is bactericidal, rapidly infused/distributed, and covers skin pathogens such as *Staphylococcus aureus* associated with SSIs.[5,6] While structurally similar to penicillin due to the β-lactam ring, different side chains result in minimal cross reactivity. Only patients who experience an IgE-mediated response (eg, anaphylaxis) or a severe cutaneous reaction (eg, Stevens-Johnson syndrome) to penicillin should avoid future cephalosporins.[5] The primary objective of our study was to determine antibiotic prophylaxis selection in pediatric surgical patients with a documented penicillin ADR. Secondarily, we aimed to determine the antibiotic prophylaxis most commonly associated with perioperative adverse drug events (ADEs).

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Materials and methods

Population and setting

A retrospective study was performed extracting data from a surgical bundle reliability report for the period from January 1, 2011, to December 31, 2013. The surgical bundle reliability report is generated from the hospital electronic medical records as a part of a national quality improvement collaborative. All operating room procedures lasting >5 minutes are included in the report. For this study, only patients who received at least 1 dose of an intraoperative antibiotic were included. The data collected included age, race, gender, surgery month/year, surgical procedure, isolation status (ie, evidence of methicillin-resistant *S. aureus* (MRSA) carrier status), wound class (ie, clean, clean/contaminated, contaminated, dirty/infected), and antibiotic(s) administered during surgery. The Children's Mercy Institutional Review Board approved this protocol.

Penicillin ADR label

Penicillin ADR type was defined as allergy or hypersensitivity or side effect, and severity was defined as follows: mild, implicated drug continued; moderate, implicated drug discontinued and/or ADR treatment required; and severe, life-threatening or need for hospitalization. ADR type and severity data were available in the electronic medical record (EMR) at the time of surgery. These data are readily available to prescribers; however, attention to this qualifier is user dependent and likely variable. Documentation of penicillin ADRs included any of the following antibiotics: amoxicillin, oxacillin, penicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, piperacillin-tazobactam. Patients with a penicillin allergy or hypersensitivity but undocumented severity were included as 'unknown' severity. Patients with a documented cephalosporin ADR were excluded.

Potential perioperative adverse drug event (ADE)

Potential perioperative ADEs were based on *International Classification of Diseases, Ninth Revision, Clinical Modification*

(ICD-9-CM) diagnostic codes (Table 1). ADE codes were selected from an extensive list of the National Expert Panel of the ICD-9-CM Adverse Event Classification, Utah/Missouri Patient Safety Consortium and from codes used by our active hospital pharmacovigilance program to identify ADEs.[7,8] Those codes considered pertinent to antibiotic-associated ADEs were included. Patients who had an ADE-associated ICD-9 code or E-code at either the point of discharge following the initial surgical procedure or during a subsequent hospitalization (if readmission occurred within 48 hours of the initial surgical procedure) were considered to have potentially experienced a perioperative ADE.

Data analysis

The association of penicillin ADR status with intraoperative antibiotic selection and perioperative ADEs was determined using categorical analysis; the Fisher exact test was used to determine statistical significance. A multivariable logit model was developed to determine the odds of receiving a drug other than cefazolin, adjusting for MRSA isolation and surgical wound class. All analyses were completed using Stata version 14 software (StataCorp, College Station, TX).

Results

In total, 17,741 operations with intraoperative AP were identified. We excluded 382 operations (2.2%) due to a documented cephalosporin allergy. These patients were predominately male (56%) and white (69%), with a median age of 7.6 years (interquartile range [IQR], 2.3–13.4). Most wounds were classified as clean (66%) or clean-contaminated (28%). The most common procedures were closed reduction of the elbow with percutaneous pinning, removal of hardware, and laparoscopic-assisted gastrostomy. A penicillin ADR label (allergy or hypersensitivity or side effect) was documented in 1,150 cases (6.6%). The prevalence of cefazolin administration in ADR negative (−) cases was significantly higher (86%) compared to ADR positive (+) allergy or hypersensitivity cases (28%; $P < .001$) or ADR(+) side-effect cases (48%; $P < .001$). After adjusting for MRSA isolation and wound class, the odds of receiving an alternative agent compared to ADR(−) cases, was significantly higher in ADR(+) allergy or hypersensitivity cases (25.4; 95% confidence interval [CI], 21.8–29.6) and ADR(+) side-effect cases (6.4; 95% CI, 3.8–11.0). Penicillin ADR severity had no effect on the likelihood of receiving an alternative to cefazolin.

Clindamycin was the most commonly prescribed alternative antibiotic prophylaxis among ADR(+) patients at 58.4%. This was significantly higher compared to ADR(−) patients (5.3%; $P < .001$). Penicillin ADR(+) patients also received gentamicin (4% vs 0.1%; $P < .001$) and vancomycin more frequently (2.8% vs 0.7%; $P < .001$) compared to ADR(−) patients (Fig. 1).

In total, 137 perioperative ADEs were identified, the most common were skin eruption, documented in 59 cases (43%), allergic urticaria (N = 10; 7.3%), and drug dermatitis (N = 9; 6.6%). When cefazolin was administered, there was no difference in the perioperative ADE rate between penicillin ADR(+) allergy or hypersensitivity and ADR(−) patients (1.04% vs 0.75%, respectively; $P = 0.485$). Overall, vancomycin was the antibiotic most commonly associated with a perioperative ADE, occurring in 3.3% of all cases. Penicillin ADR(+) patients experienced perioperative ADEs to vancomycin (9.7%), noncefazolin cephalosporins (5.1%), and clindamycin (0.77%).

Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) Codes Used to Identify Perioperative Adverse Drug Effects

ICD-9-CM	Description
283.9	Acquired hemolytic anemia
288.03	Drug induced neutropenia
693.0	Drug dermatitis
695.1	Erythema multiforme
708.0	Allergic urticaria
708.9	Urticaria nos[a]
782.1	Nonspecific skin eruption
995	Other anaphylactic reaction
995.1	Angioneurotic edema
995.2	Unspecified adverse effect of unspecified drug, medicinal and biological substance
995.27	Other drug allergy
995.3	Allergy, unspecified
e94.60	Local anti-infectives and anti-inflammatory drugs causing adverse effects in therapeutic use
960–961, E856–857	Poisoning by antibiotics and other anti-infectives
E930–E931	Adverse effects of antibiotics and other anti-infectives

[a]Not otherwise specified.

Discussion

Surgical antibiotic prophylaxis results in significant antibiotic exposure among children.[6,9] Despite evidence that cefazolin is safe to use in children with a non–life-threatening penicillin ADR history, many clinicians remain reluctant. Ideally, cefazolin would be selected when indicated because it is narrow-spectrum and well tolerated and has been extensively studied. Our results demonstrate that prescribers avoid cefazolin in children labeled with a penicillin ADR, regardless of the severity of the reaction. Additionally, alternative antibiotics such as vancomycin were associated with higher rates of perioperative ADRs compared to cefazolin.

In this study, penicillin ADR(+) patients received an alternative agent instead of cefazolin in 72% of cases. This is consistent with Beltran et al[9] who reported that ADR(+) children received cefazolin in only 20% of cases. We observed that penicillin ADR classification and severity did not influence antibiotic choice, suggesting that providers are not relying on ADR history to guide antibiotic selection. Clindamycin was the most common cefazolin alternative selected. Unfortunately, clindamycin has limitations due to rising resistance, making it potentially ineffective against methicillin-susceptible *S. aureus* for which cefazolin would be 100% effective.[10]

Only 1% of penicillin ADR(+) patients who received cefazolin experienced a perioperative ADE, which is consistent with previous findings.[9] Our data reveal that perioperative ADEs occurred

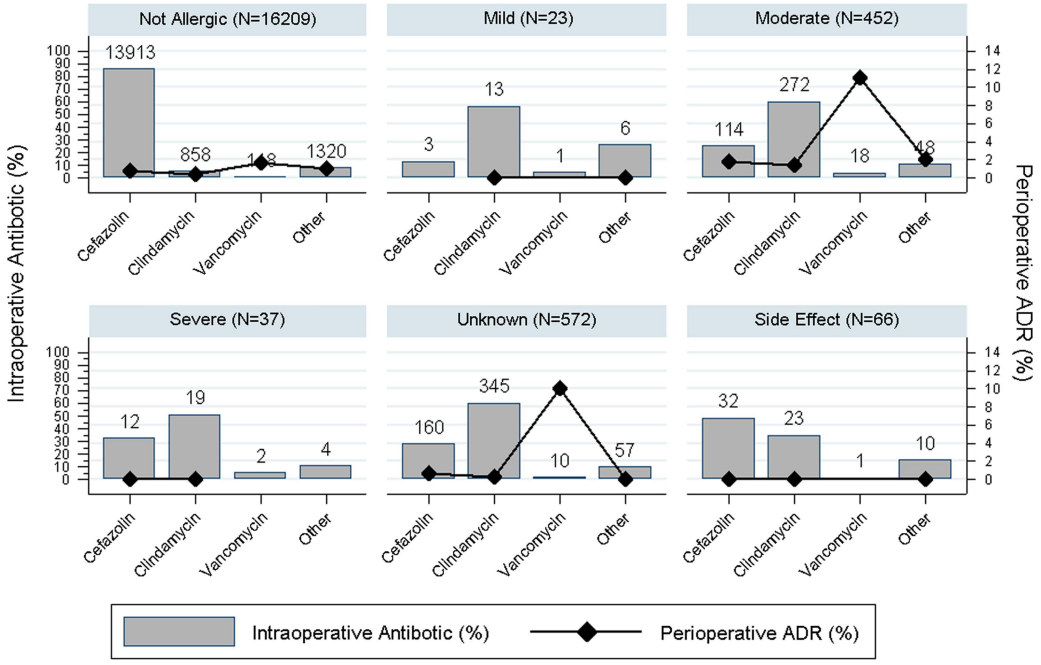

Fig. 1. Antibiotic prophylaxis exposure based on penicillin allergy classification and associated perioperative adverse drug reactions (ADR).

more frequently in ADR(+) patients who received vancomycin or alternative cephalosporins. Thus, data also highlight the finding that cefazolin alternatives are associated with a potential increased risk for perioperative ADEs.

Our study has several limitations. The findings are limited to a single pediatric institution and therefore may not be generalizable. This study was retrospective in nature, and perioperative ADEs were documented based on ICD-9-CM and E codes. Conversely, ICD-9-CM and E codes have proven effective in identifying ADEs in hospitalized patients, including surgical patients.[11,12] The selected codes were likely not all-inclusive for antibiotic-associated ADEs and could have resulted in an underrepresentation of ADEs. Attributing a perioperative ADE specifically to an antibiotic is difficult without subsequent drug rechallenge or skin testing. Most of the documented penicillin ADRs were unknown in severity, which made it challenging to determine whether cefazolin would be indicated using ADR label alone. Notably, a review of the surgical procedures included in our study's patient population revealed that many do not routinely require antibiotic prophylaxis (ie, circumcision, tympanoplasty). This finding highlights the lack of standardization for routine antibiotic prophylaxis and demonstrates that additional work is needed to limit antibiotic exposure and ADE risk for procedures without prophylaxis indications. Regardless, our data strongly indicate that perioperative antibiotic prescribing is highly variable among children with a documented penicillin ADR. Further research is needed to optimize clarification and interpretation of an ADR history to safely standardize care, to provide the antibiotic of choice when possible, and to utilize a safe alternative when truly needed.

In conclusion, our study demonstrates that surgical AP varies significantly in children with documented penicillin ADRs resulting in the unnecessary use of alternative antibiotics that result in higher rates of perioperative ADEs. Further work is needed to standardize AP selection in those labeled penicillin allergic and minimize the avoidance of cefazolin in cases when it can be safely administered.

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