Prophylactic Antibiotic Management of Surgical Patients Noted as "Allergic" to Penicillin at Two Academic Hospitals

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We studied prophylactic antibiotics administered at 2 academic medical centers during a 6-year period where a cephalosporin was indicated but an "allergy" to penicillin was noted. Another drug (typically vancomycin or clindamycin) was substituted approximately 80% of the time; this occurred frequently even when symptoms unrelated to acute hypersensitivity were listed. In >50% of cases, the reaction was either omitted or vague (e.g., simply "rash"). Given the estimated 1% cross-reactivity between penicillins and cephalosporins with similar R1 side chains, many of these patients could have received either the prescribed cephalosporin or another cephalosporin with a different R1 side chain. (A&A Case Reports. 2016;6:263–7.)

For most procedures at risk for a surgical-site infection, a drug in the cephalosporin class with high activity against the most common pathogens is the preferred antibiotic.[1] Although surgeons are accountable for the ordering of prophylactic antibiotics, at many hospitals, for logistical considerations, anesthesiologists have assumed the responsibility for their timely administration before incision (i.e., within 2 hours for vancomycin or fluoroquinolones and within 1 hour for other drugs).[2,3]

Some providers consider the presence of any mention in the medical record of an "allergy" to a drug in the penicillin class of antibiotics[a] ("penicillin") to be a contraindication to the perioperative administration of a cephalosporin, for fear of provoking an anaphylactic reaction. This perception is likely based on older literature claiming a 10% incidence of cross-reactivity between the 2 drug classes and a subsequently disproven hypothesis that reactions are related to the presence of a common β-lactam ring.[4–7] It also should be appreciated that cephalosporins produced before 1980 were contaminated with trace amounts of penicillin, which may have been the source of some of the reported cross-reactions.[b] More recent evidence has shown that the incidence of immunologic (i.e., mediated through immunoglobulin E) cross-reactivity with first-generation cephalosporins with similar R1 side chains[c] (e.g., cefazolin) is approximately 1% and that there is no cross-reactivity with third- or fourth-generation cephalosporins.[8] First- and second-generation cephalosporins with R1 side chains that are different from the R1 side chain in penicillin are thus considered safe to administer to patients allergic to penicillin (e.g., cefotetan, cefuroxime), but second-generation cephalosporins sharing the R1 penicillin side chain (e.g., cefoxitin) are not recommended.[8] Furthermore, in 93.1% of self-reported penicillin allergy, skin tests were negative.[9] With a vague history of a reaction, 85.4% of skin tests were negative.[10] Thus, avoiding cephalosporins in the face of an unproven penicillin allergy usually is unnecessary.

Alternatives to cephalosporins, for example, clindamycin or vancomycin, have clinically important adverse effects[11,12] and cannot be safely given by IV injection over a few minutes.[d,13] Although it may be expedient to avoid cephalosporins when there is any report of a reaction to penicillin, even if an immediate hypersensitivity reaction is not described, overuse of drugs such as clindamycin or vancomycin contributes to the increasing problem of multiple drug-resistant bacteria.[14,15]

Prior to an educational effort to improve medical decision making related to prophylactic antibiotic selection when a history of a penicillin reaction is reported, we evaluated current practices at 2 large academic medical centers.

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[a]The penicillin class includes natural penicillins (e.g., penicillin G or V), antistaphylococcal penicillins (e.g., cloxacillin, dicloxacillin, oxacillin, nafcillin, methicillin), aminopenicillins (e.g., ampicillin, amoxicillin, bacampicillin, cyclacillin, hetacillin), and extended-spectrum penicillins (e.g., carbenicillin, ticarcillin, piperacillin, azlocillin, mezlocillin). Although natural penicillins are seldom administered, other drugs in the class are still in common use for indications, such as upper respiratory, middle ear, urinary tract, and soft tissue infections, and peptic ulcer disease because of *Helicobacter pylori*.

[b]Solensky R for the Work Group on Adverse Reactions to Drugs, Biologicals and Latex Committee. Cephalosporin administration to patients with a history of penicillin allergy. Available at: http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Cephalosporin-administration-2009.pdf. Accessed July 28, 2015.

[c]The R1 side chain is attached to carbon 6 of the fused β-lactam and thiazolidine rings (penicillin) and carbon 7 of the fused β-lactam and dihydrothiazine rings (cephalosporin), counting clockwise from the sulfur group.

[d]Cleocin Phosphate Package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050441s055,050639s016lbl.pdf. Accessed May 15, 2015.

METHODS

The IRBs at Thomas Jefferson University and Vanderbilt University determined that this quality improvement project did not meet the regulatory definition of human subjects research.

Reported drug reactions, sensitivities, and side effects (recorded as allergies in the electronic medical record) were extracted electronically for all surgical cases between January 2009 and December 2014 at Thomas Jefferson University Hospital (TJUH) and Vanderbilt University Medical Center (VUMC). In addition, all antibiotics administered intraoperatively and whether a cephalosporin was the preferred drug for surgical-site infection prophylaxis for the case scheduled were determined. Antibiotics were mapped electronically to generic drug names in RxNorm, as previously described,[16] and classified as penicillins, cephalosporins, vancomycin, clindamycin, or "other." Uniquely entered reactions to penicillins (1324 as TJUH and 4413 at VUMC) were examined manually and classified as: (1) allergic (symptoms associated with immunoglobulin E–mediated immediate hypersensitivity); (2) nonallergic (symptoms not indicative of a hypersensitivity reaction); (3) vague (symptoms possibly allergic, but inadequately described); (4) unknown (no reaction listed); or (5) family history (symptoms only in family members). Immediate hypersensitivity reactions included those describing anaphylaxis, angioedema, anasarca, laryngeal edema, hypotension, bronchospasm, urticaria, or pruritus. A simple description of "rash," without elaboration, was coded as a "vague" reaction. Reactions possibly indicating a delayed immunoglobulin G or immunoglobulin M response (e.g., nephritis, serum sickness, anemia, thrombocytopenia) or those clearly unrelated to an immune mechanism (e.g., headache, nausea) were characterized as nonallergic.

There were no alerts generated from the electronic health record system at either hospital when drugs were dispensed for administration by anesthesia providers or documented in the anesthesia information management system in the face of a potential drug allergy or interaction.

The prevalence of administration of each antibiotic class in the presence of a reported reaction class was calculated for the 6 consecutive 1-year periods in each hospital's data set and the mean and standard errors calculated using the method of batch means.[17–21] Two-sided Student *t* tests were applied (with Bonferroni correction for multiple comparisons), and comparison to >50% (i.e., "most") was made using the one-group, one-sided Student *t* test, requiring $P < 0.05$ to claim significance (Systat 12; Systat Software, San Jose, CA). Odds ratios with 99% confidence intervals were calculated using the mosaic package in R (version 3.2.0; The R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Descriptive Characteristics of Cases Analyzed

	TJUH	VUMC
Total cases (annual)	39,491±643	69,777±5126
Cases analyzed (annual)[a]	15,813±241	27,688±1250
Prevalence of historical reactions noted in the EHR (all cases)		
PCN "allergy" noted	12.0% ± 0.2%	13.3% ± 0.3%
CEPH "allergy" noted	0.6% ± 0.03%	2.3% ± 0.05%
Classification of PCN reactions recorded in the EHR		
Immediate hypersensitivity	37.1% ± 1.5%	33.3% ± 1.4%
Vague	30.0% ± 3.0%	30.5% ± 1.3%
Unknown or not stated	26.4% ± 5.2%	26.6% ± 2.3%
Nonimmunologic	6.1% ± 0.2%	9.1% ± 0.4%
Family history only	0.3% ± 0.02%	0.5% ± 0.03%

CEPH = cephalosporin; EHR = electronic health record; PCN = penicillin; TJUH = Thomas Jefferson University Hospital; VUMC = Vanderbilt University Medical Center.

[a]Received antibiotic for surgical-site infection prophylaxis, cephalosporin first-line antibiotic, not allergic to cephalosporins.

RESULTS

The prevalence in the electronic health record of reactions to penicillins or cephalosporins (reported as allergies) was similar at TJUH and VUMC (12.0% and 13.3%, respectively; Table 1). Only 37% and 33% of cases at TJUH and VUMC, respectively, in which a penicillin allergy was reported listed symptoms compatible with an immediate hypersensitivity reaction (Table 1). In >50% of cases at both hospitals, descriptions of penicillin reactions were inadequate (i.e., vague or not recorded) to determine whether they represented a possible allergy (Table 1, $P = 0.006$ [TJUH] and $P = 0.001$ [VUMC]).

In the presence of any recorded reaction to penicillin, providers at VUMC were >3 times as likely to administer a cephalosporin as those at TJUH for cases in which a cephalosporin was first-line therapy for antibiotic prophylaxis, an antibiotic was administered, and the patient was not noted as allergic to cephalosporins (Table 2). When an alternative to a cephalosporin was chosen, providers at TJUH were more likely to administer vancomycin than those at VUMC and less likely to administer clindamycin (Table 2). The latter 2 findings may represent institutional preferences or a greater case mix of orthopedic surgery at TJUH compared to VUMC. At both institutions, providers were more likely to administer a cephalosporin when the reaction described had a nonimmunologic basis than when the reaction was nonallergic, vague, or not stated (Fig. 1). Even when symptoms reported to penicillin were nonallergic and a cephalosporin was indicated, in <40% of cases was a cephalosporin administered at either hospital (Fig. 1).

Of 5021 cases at VUMC in the data set where a cephalosporin was administered in the presence of a reported allergy to penicillin, no allergic reactions were reported in the intraoperative complications database. Overall, at VUMC, among 187,919 cases where a cephalosporin was administered intraoperatively, 24 allergic reactions were noted, only 9 of which were characterized as anaphylaxis. However, the substance responsible for the allergic reaction could not be determined from the database, so the prevalence of allergic reactions to cephalosporins at most was 0.02% (the 95% binomial upper confidence limit, assuming, unrealistically, that every reaction was due to a cephalosporin). Similarly, of 1046 cases at TJUH where a cephalosporin was administered with a penicillin allergy noted, no allergic reactions were noted in the intraoperative complications database. Only 1 questionable case of anaphylaxis was noted in 21,505 cases in which a cephalosporin was administered intraoperatively (95% binomial upper confidence limit = 0.03%). At both institutions, entry in the database of the occurrence or lack of occurrence of any intraoperative complication was close to 100%.

Table 2. Differential Behavior of Providers with Any Penicillin Reaction Noted in the EHR

Antibiotic administered[a]	TJUH (mean ± SE)	VUMC (mean ± SE)	Odds ratio VUMC:TJUH (99% CI)
Cephalosporin	6.5% ± 0.4%	20.4% ± 0.7%	3.65 (3.30–4.03)
Clindamycin	39.2% ± 1.07%	58.9% ± 2.1%	1.41 (1.33–1.50)
Vancomycin	49.9% ± 0.9%	18.9% ± 0.5%	0.24 (0.22–0.25)

CI = confidence interval; EHR = electronic health record; SE = standard error; TJUH = Thomas Jefferson University Hospital; VUMC = Vanderbilt University Medical Center.

[a]Denominators are cases in which the patient was listed as allergic to penicillin, an antibiotic was administered, the first-line drug was a cephalosporin, and the patient was not noted to be allergic to cephalosporins.

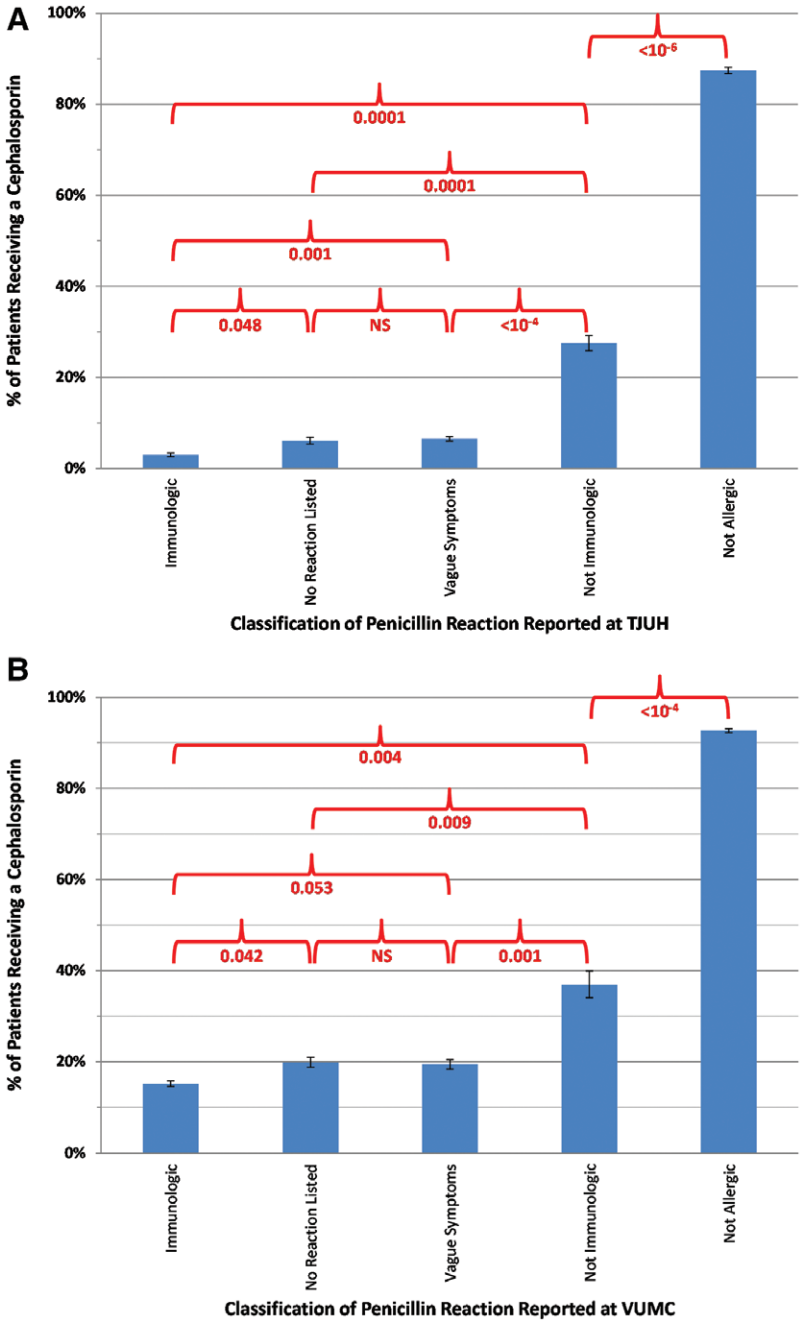

Figure 1. Cephalosporin administration in the context of a reported previous reaction to penicillin. The percentage of cases at Thomas Jefferson University Hospital (A) and Vanderbilt University Medical Center (B) during which patients received a cephalosporin, when indicated for surgical site infection prophylaxis, according to the class of historical reaction to penicillin noted in the electronic medical record. *P* values are provided for contrasts (red brackets with associated *P* values) within the groups with a Bonferroni correction applied for 6 multiple comparisons. Providers did not distinguish substantively among allergic, unknown, or vague reactions, with similar prevalences of cephalosporin administration within institutions. In the presence of nonallergic reactions to penicillin, there was a greater tendency to administer a cephalosporin compared with other reactions, but the overall rate was still low.

DISCUSSION

This case report describing the experiences at 2 large, academic medical centers highlights several major problems related to the choice of antibiotic when a cephalosporin is indicated for surgical-site prophylaxis and a historical reaction to penicillin is noted in the medical record. First, symptom descriptions in the electronic health record usually were inadequate to assess whether a patient was at risk for an anaphylactic reaction. Although electronic health systems could do more to encourage providers to better characterize drug reactions (e.g., requiring characterization of a rash as urticarial, if known), this may be of limited utility, given that patient self-reporting of penicillin allergies has poor predictive value when assessed by subsequent skin testing.[9,10] Nonetheless, separating side effects, drug sensitivities, and allergic symptoms would likely aid medical decision making when antibiotic choices need to be made in the presence of a prior reaction, especially when clinical decision support related to medication prescribing is involved.

Second, there was a substantial prevalence of providers electing to administer an alternative antibiotic rather than the indicated cephalosporin even in the face of reactions that have no immunologic basis. Because the concern of administering a cephalosporin to a penicillin-allergic patient relates to the risk of causing an anaphylactic reaction, it is not logical to substitute antibiotics when the penicillin reaction reported is not indicative of an immediate hypersensitivity reaction. First- and second-generation cephalosporins with R1 side chains differing from that found in penicillin have minimal risk, even in penicillin-allergic patients, so in the face of ambiguity, their use should be strongly considered. For example, cefuroxime, a second-generation cephalosporin with a different R1 side chain than penicillin, is an effective alternative to cefazolin for antimicrobial prophylaxis.[22] Cefoxitin, another second-generation cephalosporin indicated for prophylaxis during colorectal surgery,[22] also has a different R1 side chain than penicillin.

There are substantial opportunities to improve prophylactic antibiotic selection in the face of reported allergies to penicillin in the electronic medical record and also for vendors to improve the characterization of reactions to medications and other substances in their electronic health record systems. Education of both anesthesia providers and their surgical and nursing colleagues will be necessary to overcome the bias to avoid all cephalosporins when a penicillin allergy is reported, regardless of the nature of the reported reaction. Given the extremely low prevalence of an intraoperative allergic reaction in patients who received a cephalosporin at either study hospital, and the absence of any anaphylactic reactions noted in patients receiving a cephalosporin in the presence of a penicillin allergy, we think that reconsideration of the current process is both safe and appropriate. The substitution of vancomycin or clindamycin for a cephalosporin when a penicillin allergy is noted is an important decision that should be carefully considered. Appropriate choice of antibiotics is critical to antibiotic stewardship,[e] an area that is of increasing importance in the face of the alarming increase of microbial drug resistance. ■

[e]Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. Available at: http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed May 18, 2015.

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