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Screening for Beta-Lactam Allergy in Joint Arthroplasty Patients to Improve Surgical Prophylaxis Practice

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ABSTRACT

Background: The reliability of patient-reported penicillin allergies has been disputed. A Drug Allergy Clinic (DAC) was established at our institution in combination with an electronic best practice alert (BPA) in the Orthopedic Clinic. Joint arthroplasty patients with a reported history of beta-lactam allergy (HOBA) were preoperatively referred via the BPA to the DAC. The purpose of this study was to determine the effectiveness of beta-lactam allergy screening in enabling the surgical team to optimize antimicrobial prophylaxis.

Methods: Between February 2013 and May 2015, 161 patients with a HOBA were referred to the DAC where they underwent penicillin skin testing (PST), a drug challenge to a beta-lactam antibiotic, and/or had no intervention depending on the history obtained.

Results: PST was performed on 140 of 161 (87%) patients. A negative PST was noted in 139 (99%) patients, indicating no penicillin allergy. Cefazolin was safe to use in 145 (90%) patients evaluated. Significantly more patients evaluated in the DAC vs those not seen got cefazolin in any surgical prophylaxis regimen (90% vs 77%) without any adverse perioperative reactions. Concurrently, the use of non-beta-lactam antibiotics was significantly less in the patients evaluated vs not evaluated (16% vs 27%). The overall use of cefazolin in orthopedic surgeries in patients with HOBA was >84% over the course of the study period.

Conclusion: Beta-lactam allergy screening using a BPA and a DAC promotes the use of standard surgical prophylaxis with cefazolin. Joint arthroplasty surgeons should consider implementing allergy screening programs to promote antimicrobial stewardship.

The American Society of Health-System Pharmacists, the Infectious Diseases Society of American, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America Clinical Practice Guidelines for antimicrobial prophylaxis in surgery recommend the first-generation cephalosporin, cefazolin, for patients undergoing orthopedic spinal or joint procedures [1]. Beta-lactam antibiotics, such as penicillins and cephalosporins, are amongst the most common drugs to cause allergic reactions with prevalence rates between 1% and 10% of the general population

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[2,3]. Although cefazolin is not a penicillin derivative, it shares a similar chemical group with the beta-lactam ring. Due to this common structure, patients who are allergic to penicillin may also be allergic to cephalosporins [2]. However, the incidence of cross-reactive allergic reactions to cephalosporins among penicillin-allergic patients varies with the chemical side chain similarity of the cephalosporin to penicillin, amoxicillin, or ampicillin. For first-generation cephalosporins, the increased attributable risk is thought to be 0.4% [3]. A true, IgE-mediated allergic reaction often presents rapidly with symptoms of hives, difficulty breathing, facial or lip swelling, or low blood pressure. Yet, many patients may be inappropriately labeled as having a history of a beta-lactam allergy (HOBA) when their reaction may, in fact, have only been an adverse drug effect (ie, nausea, vomiting, or diarrhea), may have been delayed in onset and therefore not fulfilling the definition of an immediate IgE-mediated reaction, or may have occurred many years prior. Furthermore, it has been previously reported that more than 80% of patients could have diminished penicillin-specific IgE antibody over 8-10 years and that most of the reported reactions are frequently on a patient's allergy list for more than 10 years [2].

Due to time or training constraints within the medical community, medical personnel are frequently unable to obtain a detailed patient allergy history. Thus, if a patient has a reported allergy to a beta-lactam antibiotic, they are typically not prescribed this antibiotic class even when it may be medically indicated. The surgical prophylaxis recommended for total joint replacement in a patient with HOBA in place of cephalosporins is clindamycin or vancomycin with or without gentamicin depending on the need for gram-negative coverage [4]. In lieu of rising antibacterial resistance and the cost and potential adverse effects of alternative antibiotics (primarily gentamicin-associated nephrotoxicity, clindamycin-associated *Clostridium difficile* infection, and vancomycin-resistant enterococci emergence), it has become increasingly important to confirm whether a true IgE-mediated beta-lactam antibiotic allergy does indeed exist in surgical patients who report a history of such allergy.

In light of the above, the Infectious Diseases and Immunology Divisions at our institution established a Drug Allergy Clinic (DAC) in February 2013 in collaboration with the Orthopedics Department. The DAC also has a pharmacist who helps to see patients in the clinic. The role of the DAC is to evaluate patients with an upcoming joint surgery and a suspected HOBA for the presence of a true IgE-mediated hypersensitivity. Appropriate patients were identified by means of an electronic best practice alert (BPA) in orthopedic preoperative clinics. The purpose of our study was to determine the effectiveness of this new initiative at our institution in enabling the surgical team to optimize antimicrobial prophylaxis and promote antimicrobial stewardship.

Materials and Methods

Study Patients

We undertook a retrospective observational study of adult orthopedic patients (18 years and older) with a HOBA that were seen in the orthopedic total joint arthroplasty preoperative clinics at the University of Iowa Hospitals and Clinics between February 1, 2013, and March 1, 2015. This project was undertaken as a practice improvement measure at our institution. Before the start of the study, approval for database review through an expedited process was obtained from our institutional review board.

Patients were identified through an electronic BPA that triggered electronically at the time that a patient with a listed beta-lactam allergy was checked in by ancillary clinic staff (registered nurse or medical assistant) to the orthopedic clinic for determination of surgical candidacy. The BPA was designed in collaboration between the Divisions of Immunology and Infectious Diseases at our institution. The list of beta-lactam antibiotics that would trigger the BPA in a patient's allergy profile included 119 possible entries for penicillin derivatives and 116 for cephalosporins. The BPA comprised the following 2 simple questions aimed at the patient's reported HOBA: (1) the patient's initial reaction consisted only of nausea, vomiting, and/or diarrhea or (2) if the patient had taken the same beta-lactam medication uneventfully since the reaction. Orthopedic clinic staff could override the BPA for patients with HOBA who answered yes to either of the 2 questions or if the allergy had been entered in error. They were required to update a patient's allergy record if during the screening the HOBA was deemed to be non-IgE-mediated. If, however, the BPA indicated a possibility of an IgE-mediated beta-lactam allergy, the patient was referred for formal evaluation in the DAC via an electronic consult order. The supervising orthopedic practitioner for that patient was required to sign the consult order.

DAC Evaluation

Patients who were referred to the DAC were evaluated by a detailed history regarding their reported reaction(s) to beta-lactam medications, including the time that lapsed since the reaction, reason for the medication having been prescribed, nature of, time into onset and duration of the reaction, associated systemic effects, treatments given, and use of the same or similar class of medication since the reaction. If the evaluation of a penicillin allergy was suggestive of an IgE-mediated allergy, patients underwent penicillin skin testing (PST) using prick and intradermal tests to Pre-Pen (benzylpenicilloyl polylysine injection) and a penicillin G solution (by diluting to a concentration of 10,000 units/mL by taking 5 million units diluted with 500 mL of 0.9% sodium chloride injection), along with positive and negative controls [5]. If a patient had a negative PST, the standardized testing has been reported to have a 97%-99% negative predictive value for determining a penicillin IgE-mediated hypersensitivity. However, if the reaction was very suspicious for a recent IgE-mediated reaction or if the reaction was to amoxicillin or ampicillin only, the negative PST was sometimes followed by a supervised oral drug challenge to amoxicillin, as this has been shown to increase the negative predictive value of testing closer to 100% [6]. For patients, in whom the suspicion for a true IgE-mediated reaction was low, in cases where skin testing was not available (ie, some cephalosporins), if the patient refused a skin test, or would have unreliable skin testing results (due to use of antihistamines or lack of adequate response to the positive histamine control skin test), a graded supervised oral or intravenous (IV) drug challenge to a beta-lactam was performed instead of skin testing. Patients who were referred for evaluation of a history of cephalosporin allergy underwent either (1) a supervised drug challenge to IV cefazolin or the oral cephalosporin they had reacted to in the past or (2) no further testing or intervention if their reported reaction was very suggestive of a true IgE-mediated reaction. If the patient had a negative PST and/or tolerated a supervised drug challenge, the penicillin-based allergy was removed from the patient's medical record. Similarly, if skin testing was negative or supervised oral or IV drug challenge to a cephalosporin was well tolerated, the patient's allergy history was updated to reflect either the absence of a cephalosporin allergy or the specific cephalosporin that was tolerated in the drug challenge. The allergy team notified the referring orthopedic provider of the DAC outcome. Where a beta-lactam allergy was ruled out, the orthopedic provider was advised to administer cefazolin for perioperative prophylaxis for any future surgeries.

Study Design

We retrospectively collected demographic and patient-related and procedure-related data from medical records of all patients with HOBA for whom the BPA triggered during our study period. Only the data after the first BPA trigger per patient was included in the analysis, as it may have triggered at a subsequent visit. Three groups were used for comparison for the primary outcome if the HOBA listed may have been concerning for an IgE-mediated reaction: (1) patients where the BPA selection was to consult the DAC appropriately and they were subsequently seen for evaluation (consulted and evaluated group), (2) patients where the BPA selection was to consult the DAC appropriately but they were not seen for various reasons (consulted and not evaluated), and (3) patients that had the BPA overridden but would have been appropriate to be consulted based on the HOBA listed in the medical record (not consulted but should have been group). Some patients were selected to consult the DAC but were considered inappropriate consults as their HOBA listed was evident that is was an adverse effect and not an IgE-mediated reaction (ie, yeast infection to antibiotic, nausea, no personal history of HOBA but labeled due to family history, insomnia, etc.). Patient-related data included details of the HOBA if available (specific beta-lactam drug to which the reaction occurred, age at reaction, time since the reaction, quality and timing of reaction, interventions if any, and use of the same or similar drug since the reaction). For patients seen in the DAC, results of the evaluation and plan were collected. Procedure-related data included date and type of joint surgery, choice of surgical antibiotic prophylaxis, any resultant adverse reactions concerning for an IgE-mediated if cefazolin was given, and overall surgical site infections. Only the first orthopedic surgery that occurred after being evaluated in the DAC was included in the analysis.

We compared surgical antibiotic prophylaxis of patients who were appropriately referred and seen in the DAC via BPA screening with those patients who were consulted and not seen and those with a BPA override that would have been appropriate to see. We also evaluated the trend of usage of non-beta-lactam antibiotics before and after the introduction of beta-lactam allergy screening.

The following group of patients were excluded from analysis: those in whom the BPA triggered after March 1, 2015; those who were evaluated in the DAC after May 1, 2015, or after their orthopedic surgery had already occurred; those who had undergone drug allergy testing at an outside clinic; all patients with an inappropriate selection to consult the DAC based on their labeled HOBA as not being consistent with an IgE-mediated reaction; any patient who underwent a surgery that was not a knee or hip arthroplasty or revision; and all patients with an appropriately overridden BPA.

Outcomes

The primary outcome was the percentage of orthopedic patients with a history of reported penicillin or cephalosporin allergy who were able to receive the guideline-recommended surgical prophylaxis with cefazolin after evaluation in the DAC. Secondary outcomes included a comparison of antibiotic use in the 3 groups of patients who were appropriately referred and seen in the DAC via BPA screening, those who were consulted and not seen, and those with a BPA override that would have been appropriate to see.

Statistical Analysis

Statistical analysis of data was analyzed through Microsoft Excel and SAS version 9.4 (SAS Institute, Cary, NC). We compared the characteristics of patients who were consulted appropriately and evaluated in the DAC, who were consulted appropriately but were not evaluated in the DAC, and who should have been consulted but were not because the BPA was overridden. We used the chi-square test or Fisher exact test for categorical variables and Student *t*-test or the Wilcoxon rank-sum test for continuous variables. A *P* value of $\leq$.05 was considered statistically significant.

Results

The BPA fired for 363 patients seen in the orthopedics joint clinic between February 1, 2013, and March 1, 2015. Of these, 315 (87%) were deemed appropriate for referral. The BPA was selected for consultation to the DAC in 279 (77%) patients, of whom 254 were appropriate consultations. A total of 59 (16%) patients were excluded from analysis (Fig. 1). The DAC evaluated 171 patients, of whom 161 (94%) were deemed appropriate consults. Demographic characteristics (Table 1) were similar between the patients who were appropriately consulted and seen for evaluation in the DAC (n = 161), those consulted but not seen in the DAC (n = 85), and those who should have been consulted but the BPA was overridden inappropriately (n = 58). For patients not evaluated in the DAC, the information regarding their drug allergy was gathered from the documentation provided for the listed drug allergy in the electronic medical record. In the 3 groups, the average age was 64, 61, and 64 years, and 65%, 61%, and 74% were female, respectively. In the respective groups, the listed drug allergy was to a penicillin derivative in 84%, 86%, and 90% of patients, a cephalosporin in 7%, 13%, and 10% of patients, and both a penicillin derivative and cephalosporin in 9%, 1%, and none in the override group. There was a proportionally significant difference in the groups for patients who reported both a penicillin class and cephalosporin allergy ($P = .003$) and in those with other penicillin derivative allergies comprising nafcillin, dicloxacillin, and piperacillin/tazobactam ($P = .045$). The majority of the patients reporting allergies to at least 2 beta-lactam antibiotics were evaluated in the DAC. The most common HOBA reactions were rash and hives, which when combined accounted for 69%, 59%, and 81% of the reactions for each of the respective groups. The only significant difference between the groups was in the percentage of patients reporting rash ($P = .01$) and anaphylaxis ($P = .005$).

Of the 161 appropriate consults who were seen in the DAC, details of the evaluation of the HOBA are found in Table 2. The majority of patients (58%) had their reaction when they were $\geq$18 years of age and 87% had the reaction $\geq$10 years prior. Most patients (70%) did not remember when the reaction occurred in relation to the first dose of the antibiotic, only 13% recalled that it had occurred within 24 hours and only 2% recalled its occurrence within the first 2 hours. Seventy-four (46%) patients did not require any medications to treat the reaction, whereas another 40% did not remember which medication, if any had been used. Seventy-nine (46%) patients had no interventions other than stopping the medication and only 5% required emergent evaluation or hospitalization. Interestingly, 39% of patients reported taking a beta-lactam since their suspected allergic reaction without a reaction. Twenty-seven of these patients (43%) had taken a cephalosporin if allergic to a penicillin derivative and 30% had taken a penicillin derivative after a suspected penicillin allergy. In total, 54% had safely tolerated a cephalosporin after their suspected HOBA, making it potentially less concerning to administer cefazolin at the time of surgery based solely on this history.

Table 3 shows the results of patients who were evaluated in the DAC. PST was performed on 140 (87%) patients. A negative skin test occurred in 139 (99%) patients, indicating that they were not allergic to penicillin. One patient had an indeterminate PST. Twenty-one patients (13%) did not undergo PST due to their inappropriateness as consults, ineligibility for testing, or patient refusal.

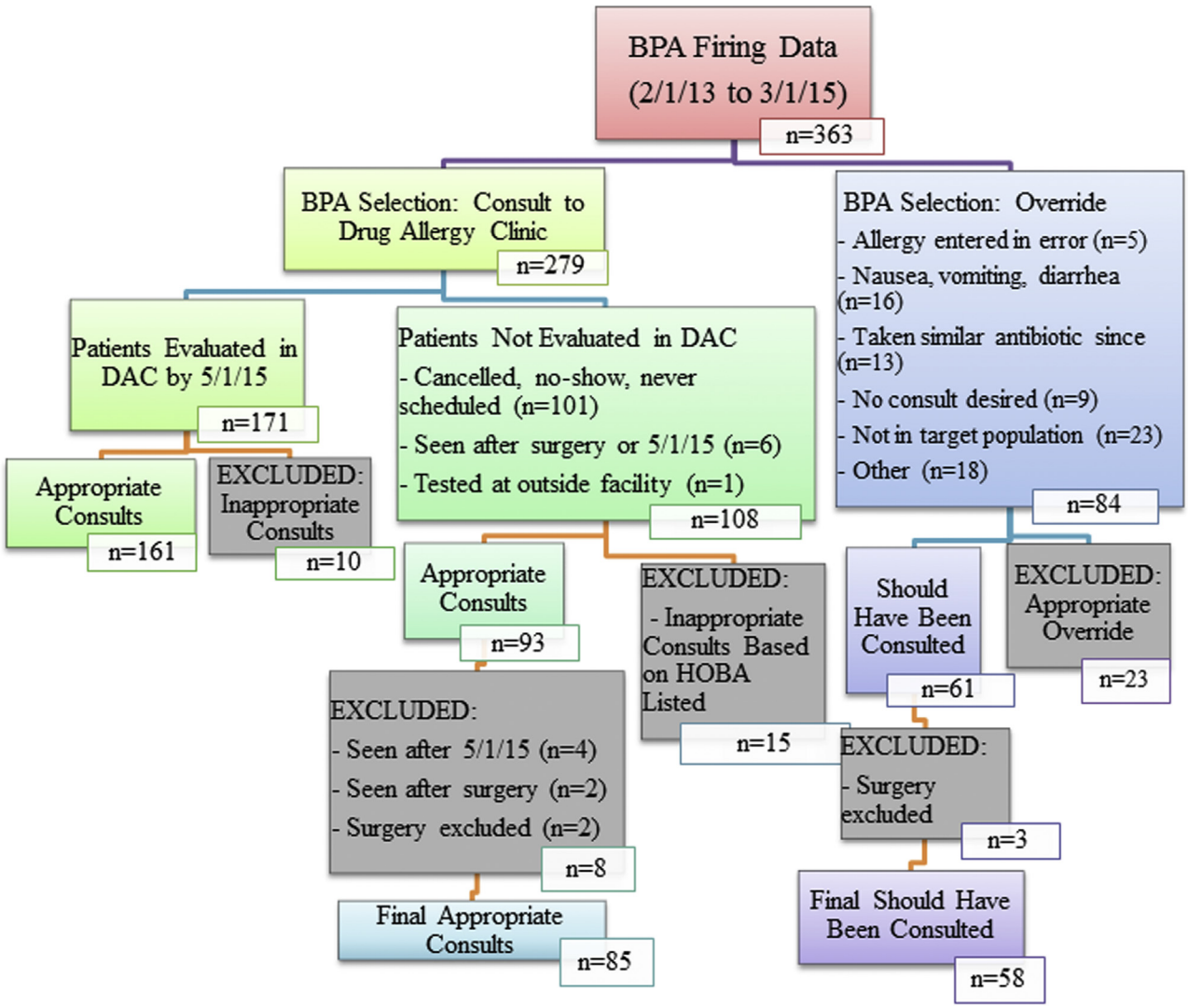

Fig. 1. Best practice alert firing data.

Only 25 (15%) patients had a supervised drug challenge, 76% subsequent to a negative PST and 24% in place of skin testing. No skin testing to cephalosporins was done. There were no reactions after the supervised drug challenges. Cefazolin was deemed safe to use in 145 (90%) patients after being evaluated. Those deemed not safe included the patient with the indeterminate PST, patients in whom a beta-lactam allergy could not be ruled out, and in those where a consistent concern for cross-reactivity with cefazolin existed. In total, 141 (88%) patients were cleared completely of the presence of a current beta-lactam allergy, whereas another 8 (5%) patients were able to be cleared of at least 1 beta-lactam allergy.

A total of 154 (96%) patients who were seen in the DAC, 58 (68%) patients who were consulted and not evaluated in the DAC, and 54 (93%) patients in the BPA override group underwent surgery (Table 4). The type of surgery and the years in which the surgery occurred was not statistically different between the 3 groups. The majority of patients in all groups received cefazolin for surgical prophylaxis. A total of 14 patients received both cefazolin and an alternative antibiotic which included clindamycin, vancomycin, and/or gentamicin. In most instances, an alternative antibiotic was given perioperatively and then cefazolin postoperatively. There was a statistical difference in the proportion of cefazolin used between the 3 groups, with more cefazolin used in the patients evaluated in the DAC ($P = .037$). The percentage of cefazolin used [illegible]y surgical prophylaxis regimen was significantly different b[illegible]en the 3 groups ($P = .005$), with the highest percentage given in 139 (90%) surgeries of patients evaluated in the DAC. Notably, in the 112 patients with a HOBA who had surgery and would have been appropriate to see in the DAC but were not seen, there was still a 72%-81% usage of cefazolin. A statistical difference remained when the use of cefazolin in any regimen was compared between the patients consulted and seen in the DAC to those consulted and not seen ($P < .001$). There was no significant difference when comparing the DAC patients to BPA overridden group ($P = .088$).

When looking at alternative antibiotic use, there was also a significant difference in the use of clindamycin ($P = .006$) and vancomycin ($P = .031$) between the groups, with more patients getting alternative antibiotics in the groups not evaluated in the DAC. There was also a statistical proportional difference in the percentage of alternative antibiotics used in any regimen with the lowest percentage in the patients evaluated in the DAC ($P = .037$). A statistical difference remained when the use of an alternative antibiotic in any regimen was compared between the patients consulted and seen in the DAC to those consulted and not seen

Table 1
Patient Demographics.

Demographics[a]	Consulted Appropriately and Evaluated in DAC (N = 161)	Consulted Appropriately but Not Evaluated in DAC (N = 85)	BPA Overridden—Should Have Been Consulted (N = 58)	*P* Value
Mean age, y (range)	64 (29-90)	61 (38-86)	64 (27-88)	.319
Female, n (%)	104 (65)	52 (61)	43 (74)	.263
Medication allergy, n (%)				
Amoxicillin	16 (10)	4 (5)	6 (10)	.326
Amoxicillin/clavulanate	1 (1)	0	0	1.000
Ampicillin	0	0	0	NA
Cephalosporin(s)	11 (7)	11 (13)	6 (10)	.274
Multiple penicillin derivatives	2 (1)	0	0	.703
Penicillin	116 (72)	66 (78)	45 (78)	.537
Penicillin class and cephalosporin	15 (9)	1 (1)	0	.003
Other penicillin derivative	0	3 (3)	1 (2)	.045
Quality of the reaction, n[b]				
Anaphylaxis	2 (1)	7 (8)	0	.005
Angioedema	19 (12)	12 (14)	5 (9)	.607
Hives	48 (30)	33 (39)	25 (43)	.127
Pruritus	13 (8)	4 (5)	4 (7)	.612
Rash	62 (39)	17 (20)	22 (38)	.01
Respiratory	11 (7)	3 (4)	2 (3)	.539
Stevens-Johnson syndrome (SJS)	2 (1)	0	0	.703
Other	19 (12)	5 (6)	5 (9)	.312
Unknown	16 (10)	9 (11)	2 (3)	.267
Underwent orthopedic surgery, n (%)	154 (96)	58 (68)	54 (93)	<.001

DAC, Drug Allergy Clinic; BPA, best practice alert; NA, not applicable.
[a] Only available data for patients not evaluated in the DAC based on the drug allergy listed in the electronic medical record.
[b] Patients may have had more than one symptom and or a different reaction(s) to more than one antibiotic. Each reaction was classified only once per patient.

($P = .012$). There was no significant difference when comparing the DAC patients to the BPA overridden group ($P = .160$).

In the 140 patients evaluated in the DAC who had surgery and were cleared to get cefazolin, 133 did receive cefazolin in any regimen. A total of 14 patients received an alternative antibiotic, either by itself or in addition to cefazolin, despite being cleared to get cefazolin. In addition, there were 6 patients evaluated in the DAC that still got cefazolin but were not cleared to get it because we were unable to fully rule out their HOBA. To our knowledge, there were no perioperative IgE-mediated reactions to cefazolin use regardless of evaluation status in the DAC.

For the patients evaluated in the DAC, the percentage of utilization of antibiotics over the time period of the study was not significantly different (Table 5). It should be noted that 2015 only covered patients seen through May 1, 2015, and was not a full year of data. Cefazolin in any regimen was 86% in 2013, 94% in 2014, and 89% in 2015 and alternative antibiotics in any regimen were 19%, 13%, and 15% over the same time frame. A preliminary review of data approximately 3 years pre-implementation of the BPA showed a 40%-70% prescribing pattern of non-beta-lactam antibiotics. When compared to post-implementation of the DAC, the use of these alternative antibiotics declined to <20% (see Table 5).

Discussion

The primary aim of this study was to improve the practice of surgical antibiotic prophylaxis in accordance with national guidelines within our institution's orthopedic department. To this end, our results demonstrate that allergy testing for penicillin allergy and/or drug challenges to cephalosporins promotes beta-lactam use for surgical prophylaxis, as the majority of such patients are not truly beta-lactam allergic. Our findings are consistent with those of several other clinical studies that have evaluated penicillin allergy testing in a wide range of surgical patients [7-11]. Our study is the first to our knowledge to demonstrate application of a preoperative clinical and electronic pathway with the goal to optimize surgical antimicrobial prophylaxis [7,8].

In our study of 363 patients with HOBA, the prevalence of reported penicillin allergy was ~12% (based on a total of ~3000 surgeries from 2013 to 2015) which is slightly higher than published rates of 1%-10% of the general population. One hundred and forty (87%) patients seen in the DAC underwent PST and except for 1 patient with an indeterminate result, rest had a negative skin test. Of the 154 patients who were seen in the DAC and had surgery, 133 (86%) were cleared to get cefazolin. For the patients seen in the DAC vs those patients who were consulted but not seen, there were a significantly higher percentage who received cefazolin and statistically lower percentage who received an alternative antibiotic. This indicates that the DAC evaluation was important in guiding the surgical team in the optimal prescribing of prophylactic surgical antibiotics. A preliminary review of the percent usage of non-beta-lactam antibiotics at our institution before and after drug allergy screening demonstrated a decrease which was consistent with published literature. Li et al [10] in their study of 60 orthopedic patients with HOBA demonstrated that 6 of 55 (11%) patients who had undergone penicillin allergy skin testing and subsequent surgery received vancomycin compared to 38 of 127 (30%) of historical controls. Park et al [8] also reported a benefit of a preoperative allergy clinic in reducing vancomycin for prophylaxis purposes in patients with HOBA and showed a decline in vancomycin use from 30%-16% in their study of 1111 patients following their intervention. This reduction in the use of non-beta-lactam prophylactic regimens is important because non-beta-lactam drugs, such as vancomycin, gentamicin, and clindamycin used as monotherapy do not provide the combined gram-positive and gram-negative antibacterial activity in prophylaxis needed to prevent surgical site infections, that cefazolin does. Although broad antibacterial coverage can be achieved through a regimen of vancomycin and gentamicin, this drug combination has potential toxicities of ototoxicity and nephrotoxicity. This is particularly relevant to the type of patients undergoing joint arthroplasty who are frequently elderly with multiple comorbidities including diabetes, obesity, and chronic kidney disease. The latter are all conditions that increase the risk of drug toxicity and subsequently lead to longer hospital stays and readmission rates.

Table 2
History of Beta-Lactam Allergy Specifics After Evaluation in the DAC.

Drug Allergy History	Appropriate Patients Evaluated in DAC (N = 161)
Age reaction, y (%)	
<18	60 (37)
≥18	93 (58)
Unknown	8 (5)
Time since reaction, y (%)	
<1	1 (1)
1-5	7 (4)
6-10	7 (4)
>10	139 (87)
Unknown	7 (4)
Time of reaction into antibiotic, h (%)	
<2	4 (2)
2-24	17 (11)
24-48	6 (3)
>48	22 (14)
Unknown	112 (70)
Medications required for treatment, n (%)	
Antihistamines	15 (9)
Corticosteroids	3 (2)
Epinephrine	2 (1)
None	74 (46)
Other	3 (2)
Unknown	64 (40)
Interventions required, n (%)	
Hospitalized	2 (1)
Seen in clinic	30 (19)
Seen in emergency room	6 (4)
None	79 (49)
Unknown	44 (27)
Taken similar antibiotic, n (%)	
No	75 (47)
Unknown	23 (14)
Yes	63 (39)
PCN if allergy to PCN	19 (30)
PCN if allergy to cephalosporin	8 (13)
PCN if allergy to both	2(3)
Cephalosporin if allergy to cephalosporin	0
Cephalosporin if allergy to PCN	27(43)
Cephalosporin if allergy to both	2 (3)
Both if allergy to PCN	4(6)
Both if allergy to cephalosporin	1(2)

DAC, Drug Allergy Clinic; PCN, any penicillin derivative.

Table 3
Results From DAC Evaluation.

DAC Evaluation	Consulted Appropriately (N = 161)
Year seen in DAC, n (%)	
2013 (2/1/13 to 12/31/13)	74 (46)
2014 (1/1/14 to 12/31/14)	66 (41)
2015 (1/1/15 to 5/1/15)	21 (13)
PST, n (%)	
Yes	140 (87)
No	21 (13)
No adequate positive control	6 (29)
Cephalosporin allergy only	9 (42)
Chronic urticaria	1 (5)
Patient declined	1(5)
Ruled out with history	4 (19)
Results of PST, n (%)	(N = 140)
Negative	139 (99)
Indeterminate	1 (1)
Positive	0
Supervised drug challenge, n (%)	
No	136 (85)
Yes	25 (15)
Done in place of PST	6 (24)
Done in addition to PST	19(76)
Adverse reactions	0
Beta-lactam used in drug challenge, n (%)	(N = 25)
Amoxicillin	10 (40)
Penicillin	3 (12)
Cefazolin	4 (16)
Cephalexin	7 (28)
Other cephalosporin	1 (4)
Final allergy diagnosis, n (%)	
No PCN allergy	133 (83)
No cephalosporin allergy	4 (2)
No PCN, but unable to rule out cephalosporin	3 (1)
Both PCN and cephalosporin removed	4 (2)
IgE-mediated reaction confirmed	1 (1)
No testing completed	9 (6)
Severe reaction suspected so continue to avoid	2 (1)
Other	5 (3)
Cleared to get cefazolin for surgery, n (%)	
Yes	145 (90)
No	15 (10)
Concern for severe reaction with cefazolin	3 (20)
Could not rule out beta-lactam allergy	11(73)
Indeterminate PST	1(7)

DAC, Drug Allergy Clinic; PCN, any penicillin derivative; PST, penicillin skin testing.

Study Strengths

Our allergy screening program is a good example of interdisciplinary collaboration to improve quality of patient care. By establishing a simple, preoperative screening tool, we were able to bypass the need for surgical staff to obtain a detailed allergy history when they are not expected to have a thorough knowledge of drug allergies. At the same time, our simple, 2-question-based BPA allowed orthopedic ancillary staff to perform basic screening of patients with HOBA for purposes of referral for allergy consultation as well as remove the beta-lactam allergy from patients' records in cases of non-IgE-mediated reactions.

In our DAC, the role of a pharmacist was instrumental to the allergy screening process. We believe that even in low-tier hospitals where an allergy consultative service may not be readily available, the incorporation of a simple screening BPA in the preoperative workflow and appropriate guidance from a pharmacist could help surgeons determine the safety of beta-lactams for surgical prophylaxis. Where allergy specialists are readily available, a clinical and electronic pathway consisting of BPA screening of patients with HOBA followed by formal allergy evaluation and PST or drug challenge could enable surgeons to make more accurate decisions regarding antimicrobial surgical prophylaxis.

We are not aware of any perioperative adverse reactions to cefazolin in either the screened patients or those who had a suspicious HOBA but were not seen in the DAC for various reasons. Of note, among the latter untested group, 72%-81% patients nevertheless received cefazolin and tolerated it well. Our orthopedic surgeons prescribed cefazolin prophylaxis to this subgroup of patients based on their growing awareness from our study of the low likelihood of cross-reactivity between cefazolin and penicillin. This reinforces what is widely advocated by allergy specialists that most adult patients' HOBA is inaccurate due to recall bias, a very remote history of a hypersensitivity penicillin reaction (>10 years old) or a history of adverse drug reactions that were in fact not IgE-mediated or even penicillin related and that cross-reactions between cephalosporins and penicillins are very low [4,12]. Our observations are consistent with the work of others and call for an urgent need to educate surgical teams, including anesthesiologists regarding cefazolin administration in penicillin-allergic patients [7,8,10,11]. Having said that, we strongly advocate the need for evaluation of beta-lactam allergies before prescribing them in patients with a history suggestive of an IgE-mediated reaction.

Table 4
Surgical Data.

Surgery Data	Consulted Appropriately and Evaluated in DAC (N = 154)	Consulted Appropriately but Not Evaluated in DAC (N = 58)	BPA Overridden—Should Have Been Consulted (N = 54)	*P* Value
Type of surgery				.151
Knee arthroplasty	85 (55)	30 (52)	17 (31)	
Hip arthroplasty	69 (45)	28 (48)	37 (69)	
Year of surgery, n (%)				.526
2013	59 (38)	20 (35)	26 (48)	
2014	68 (44)	24 (41)	21 (39)	
2015	27 (18)	14 (24)	7 (13)	
Perioperative antibiotics, n (%)				
Cefazolin	130 (84)	40 (69)	41 (76)	.037
Cefazolin/gentamicin	0	1 (2)	0	.421
Cefazolin/vancomycin	9 (6)	1 (2)	3 (6)	.499
Clindamycin	3 (2)	7 (12)	4 (7)	.006
Vancomycin	0	2 (3)	2 (4)	.031
Vancomycin/gentamicin	12 (8)	7 (12)	4 (7)	.575
Cefazolin use in any regimen, n (%)	139 (90)	42 (72)	44 (81)	.005
Alternative antibiotics used in any regimen, n (%)	24 (16)	18 (31)	13 (24)	.037
Antibiotics based on DAC evaluation, n (%)[a]				
Cefazolin, cleared to receive	133 (86)	NA	NA	NA
Cefazolin, not cleared to receive	6 (4)	42 (72)	44 (81)	NA
Alternative antibiotic, cleared for cefazolin	14 (9)	NA	NA	NA
Alternative antibiotic, not cleared for cefazolin	10 (7)	18 (31)	13 (24)	NA

DAC, Drug Allergy Clinic; BPA, best practice alert; NA, not applicable.
[a] Patients who got an alternative antibiotic in addition to cefazolin were classified as getting both.

In our study, all patients who were cleared for beta-lactam allergy had their allergy record updated by the allergy team, in addition to clear documentation of the allergy evaluation and notification of the referring orthopedic surgeon. This allowed for quality improvement and patient safety. Beta-lactam allergy testing also promotes antimicrobial stewardship for future purposes as it allows the therapeutic use of beta-lactam drugs when these are indicated as the first-line of treatment. Our study was not designed to address the impact of negative beta-lactam allergy testing on future hospitalizations for infections or surgery; however, we anticipate that the long-term impact would be quite significant, especially given the alarming rates of antimicrobial resistance and paucity of new antibiotics in the therapeutic pipeline [13].

Limitations

Our study has several limitations. It included only orthopedic surgical patients and was conducted at an academic tertiary care center. However, based on similar published studies in nonorthopedic patients, a preoperative beta-lactam allergy screening program such as ours is expected to be beneficial to all surgical specialties [7,9,14]. We acknowledge that the allergy screening and testing protocol may be difficult to implement in smaller hospitals. However, as mentioned above, a concerted effort toward education of surgical and nursing staff and creating an electronic BPA under the supervision of a pharmacist could enable effective screening of patients with HOBA.

The biggest limitation of our study was the inability to evaluate a considerable number of patients in the DAC despite their having had a suspicious HOBA for an IgE-mediated allergy (n = 143). This group included those who were deemed eligible for referral by the BPA to DAC but were ultimately not seen (n = 85) and those in whom the BPA was overridden by orthopedic nursing staff for what may have been inappropriate reasons (n = 58). Interestingly, 8% of patients in the consulted and not seen group had a reaction listed as anaphylaxis and should have been seen in the DAC before being given beta-lactam prophylaxis. Attributable reasons for why all these patients were not seen in the DAC included nursing error in not placing an electronic consult to the DAC, administrative errors in scheduling appointments, and nursing misinterpretation of the BPA questions.

At the introductory stages of our screening program, surgical staff and patients alike were frustrated that the screening process did not consolidate same-day preoperative and allergy appointments. This inability was due to administrative limitations and/or a need for patients to discontinue antihistamines for at least 5 days before PST. As our protocol established itself, we were able to coordinate almost all DAC evaluations with preoperative orthopedic appointments.

Table 5
Post-BPA Surgical Prophylaxis in Patients Evaluated in DAC.

Presurgical Antibiotic Data[a]	2013 Feb-Dec (N = 59)	2014 Jan-Dec (N = 68)	2015 Jan-Mar (N = 27)	*P* Value
Perioperative antibiotics, n (%)				
Cefazolin	48 (82)	59 (87)	23 (85)	.700
Cefazolin/vancomycin	3 (5)	5 (7)	1 (4)	.818
Clindamycin	2 (3)	1 (1)	0	.775
Vancomycin/gentamicin	6 (10)	3 (4)	3 (11)	.403
Cefazolin in any regimen, n (%)	51 (86)	64 (94)	24 (89)	.335
Alternative antibiotics used in any regimen, n (%)	11 (19)	9 (13)	4 (15)	.700

DAC, Drug Allergy Clinic; BPA, best practice alert.
[a] Data are for patients evaluated in the DAC from February 1, 2013, through March 1, 2015.

Future Directions

Because there were a considerable number of patients who were not seen in DAC in spite of their having a suspicious HOBA and being deemed eligible by the BPA for a referral, it would be important to address gaps in the understanding of the BPA questions among the surgical clinic nursing staff. Efforts have been

made to discuss the orthopedic clinic workflow with the surgical and nursing staff in order to refine this process.

In light of the changing landscape in Medicare reimbursements for joint arthroplasty patients from fee-for-service to episode-of-care models, it would be important to ascertain how the costs of an allergy screening program such as ours would be incorporated in a bundled payment initiative [15,16]. Certainly, closer collaboration between orthopedic surgeons, pharmacists, and allergy specialists in the functioning of such a screening program could prove to be cost-effective for hospitals and patients alike, both in the short term as a result of reduced use of vancomycin prophylaxis and in the long term, by increasing the therapeutic use of beta-lactams in place of alternative and often unnecessarily broad-spectrum antibiotics.

Ultimately, we hope to evaluate in greater detail the impact of the overall use of cefazolin in orthopedic surgical patients with HOBA since implementation of the BPA and DAC and compare to usage rates at least 3 years preintervention. In addition, we plan to undertake a larger study to look at the broader impact of this protocol on surgical site infections and nosocomial infection rates of vancomycin-resistant enteroccoci and *Clostridium difficile* from a reduction in non-beta-lactam prophylaxis as well as cost-savings from decrease in vancomycin use.

Conclusions

Our study reinforces the benefits of preoperative beta-lactam allergy testing and highlights the fact that the majority of patients with HOBA do not have true IgE-mediated beta-lactam allergy. Of the patients with HOBA evaluated in the DAC, 88% were cleared completely of their beta-lactam allergy and 93% of at least 1 beta-lactam allergy. Thus, the use of standard surgical prophylaxis with cefazolin was deemed safe in 91% of patients. A simple electronic screening tool such as a BPA can be used by orthopedic surgical teams to identify patients with HOBA who would benefit from allergy consultation and penicillin allergy skin testing or other beta-lactam challenge. Such a strategy would enable surgeons to make informed decisions regarding antimicrobial surgical prophylaxis and promote antimicrobial stewardship for perioperative and future purposes.

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