

# A Simple Algorithmic Approach Allows the Safe Use of Cephalosporin in “Penicillin-Allergic” Patients without the Need for Allergy Testing

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**Background:** Patients who report a penicillin allergy are often given second-line antibiotic prophylaxis during total joint arthroplasty (TJA), with only a minority of patients undergoing additional consultations and allergy testing. In an effort to increase the use of cephalosporin prophylaxis in TJA, the present study aimed to assess the effectiveness of a simple, protocol-driven penicillin allergy screening program without the need for additional work-up.

**Methods:** Following implementation of a questionnaire-based screening protocol in May 2019, all patients scheduled for primary TJA were risk-stratified into low or high-risk categories. The low-risk cohort received cefazolin, and the high-risk cohort received non-cefazolin antibiotics. Patients were monitored prospectively, and data on antibiotic usage and adverse outcomes were documented. The protocol group (n = 2,078) was propensity score matched 1:1 with a control group that included patients who underwent TJA in the same institution prior to implementation of the protocol. The primary end point was the efficacy of the protocol in reducing unnecessary use of non-cephalosporin antibiotics for prophylaxis. Secondary outcomes included the rate of surgical site infections and allergic reactions to the administered antibiotic.

**Results:** A total of 357 patients (17.2%) reported a penicillin allergy in the protocol group compared with 310 patients (14.9%) with a recorded allergy in the control group (p = 0.052). The number of patients who received non-cephalosporin antibiotics was significantly lower in the protocol group (5.7% compared with 15.2% in the control group; p < 0.001), whereas there was no difference in the rate of total allergic reactions (0.8% compared with 0.7%, respectively; p = 0.857). Of the 239 low-risk patients (66.9%) in the protocol group, only 3 (1.3%) experienced a mild cutaneous reaction following cefazolin administration. There were no differences in the rates of superficial wound, deep periprosthetic, or *Clostridioides difficile* infections between the protocol and control groups.

**Conclusions:** A simple screening protocol allowed two-thirds of patients with a self-reported allergy to receive cefazolin without the need for additional consultations or testing. We believe this protocol can be safely implemented to increase the rate of cefazolin usage without a corresponding increase in the number of allergic reactions.

**Level of Evidence:** Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

Perioperative antibiotic prophylaxis prior to total joint arthroplasty (TJA) is considered standard care<sup>1</sup> and has been shown to reduce the rate of surgical site infection<sup>2</sup>. Official guidelines from the American Academy of Orthopaedic Surgeons and other organizations recommend the use of first- or second-generation cephalosporin antibiotics because of their favorable side-effect profiles and efficacy against the majority of organisms associated with surgical site infections<sup>3,4</sup>.

Despite their widespread utility, beta-lactam antibiotics, including penicillins and cephalosporins, are the most common antibiotics reported to cause reactions (including both adverse effects and true allergies), often limiting their usage<sup>5</sup>; however, the reliability of self-reported antibiotic allergies is extremely low<sup>6</sup>. Furthermore, although a 10% cross-reactivity among beta-lactams (wherein 1 of 10 patients with an allergy to penicillin would have an allergic reaction to a cephalosporin) has historically been a concern, this rate has been attributed to

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the contamination of pre-1980 cephalosporins with trace amounts of benzylpenicillin, resulting in a gross overestimation of the degree of cross-reactivity<sup>7</sup>. Current evidence suggests that the prevalence of clinically relevant immunologically-mediated cross-reactive allergic reactions is <1%<sup>8-11</sup> and could be even lower in cephalosporins with different side-chain determinants<sup>7</sup>. Nonetheless, these allergy labels have been shown to drive arthroplasty surgeons to use alternative antibiotics<sup>12</sup>, which have been associated with a higher risk of surgical site infections, increased antimicrobial resistance, and higher costs<sup>2,6,13-17</sup>.

Few studies have proposed interventions to increase the use of cefazolin in TJA patients with a self-reported history of penicillin allergy<sup>13,18</sup>. Previous studies utilized complex algorithms that often necessitated additional consultations and allergy testing, which could in turn delay surgery and increase overall costs<sup>19</sup>. More importantly, recommending that penicillin-allergic patients should have cephalosporin-tolerance testing prior to therapeutic use may not improve patient safety or clinical outcomes because of the high “number needed to treat” (i.e., the number of patients who would need to be treated in order to achieve a minimal hypothetical benefit)<sup>20</sup>, which, taken together with the low likelihood of such testing occurring, could conversely result in an increased use of second-line, non-cephalosporin antibiotics.

The present study aimed to assess the effectiveness of a simple, protocol-driven penicillin-allergy screening program for patients with a self-reported history of penicillin allergy undergoing TJA at a large orthopaedic practice. We hypothesized that this would lead to a significant decrease in the usage of non-cephalosporin antibiotics for prophylaxis.

## Materials and Methods

From May 2019 to July 2020, a questionnaire-based allergy protocol was implemented at a single institution. All total knee arthroplasty (TKA) and total hip arthroplasty patients were monitored prospectively for the type of antibiotic utilized during their care and for any consequent allergic reactions. Only patients who received cefazolin, vancomycin, or clindamycin as antibiotic prophylaxis for surgery were screened for inclusion. Patients who had prophylaxis with an antibiotic other than the 3 specified and those without information regarding the type of prophylactic antibiotic were excluded from the study (Fig. 1). The study was approved by the institutional review board.

## Protocol

The protocol was developed by a multidisciplinary team consisting of surgeons, medical consultants, and pharmacists. As part of the screening protocol, patients were educated by a team of nurses at the preadmission testing center with a handout explaining the low incidence of a true immunoglobulin-E (IgE)-mediated allergic reaction among patients labeled with a penicillin allergy (Fig. 2). Subsequently, a questionnaire adapted from the American Medical Association Penicillin Allergy Toolkit<sup>21</sup> was administered by trained preadmission testing staff who were not involved in the study. Primarily, patients were asked to

declare if they had a history of penicillin allergy. Patients declaring a penicillin allergy were then queried as to the details of the reaction (see Appendix 1). Patients were stratified into low-risk and high-risk groups (Fig. 3). Low-risk patients had cefazolin administered intravenously at a dose of 1 g (for those <80 kg) or 2 g (for those ≥80 kg) prior to skin incision and were closely monitored perioperatively for signs and symptoms of hemodynamic compromise and allergic reaction by the anesthesiology team. High-risk patients had vancomycin administered at 15 mg/kg or clindamycin administered at 900 mg. Postoperatively, all patients received 2 doses of cefazolin every 8 hours or 1 dose of vancomycin every 12 hours, and all antibiotics were discontinued within 24 hours postoperatively. If patients met discharge criteria, they did not have to complete the 24 hours of antibiotic therapy before discharge. Antibiotic-loaded cement was not routinely utilized by any surgeon in this study. All procedures were inpatient procedures, and no outpatient TJA was performed. Patients were observed during their hospitalization stay for any delayed symptoms and were provided with a number to call if they experienced any symptoms of allergy following discharge. Any allergic reaction was then recorded in the patient chart. Access to standard medications for the treatment of allergic reactions was ensured throughout the perioperative course. Patients who were successfully administered cefazolin without a reaction were given a letter stating the tolerance to cefazolin with the dose specified, in the event that the patient wished to further investigate or receive prophylaxis with a cephalosporin in the future.

The primary end point of the study was the efficacy of the protocol in reducing the use of non-cephalosporin antibiotics for prophylaxis. Secondary end points included the safety of the protocol as determined by the number of allergic reactions to the antibiotics utilized, as well as the risk of surgical site and *Clostridioides difficile* infection. For comparison, a control group consisting of patients who underwent surgery before the implementation of the protocol (from January 2016 to April 2019) was matched in a 1:1 fashion with use of propensity scores. Propensity score matching provided a method to control for selection bias and ensure covariate balance between the groups by matching each patient in the study period with a patient in the early period who had the most similar patient characteristics (i.e., nearest-neighbor matching). Specifically, propensity scores generated with use of logistic regression were utilized to adjust for the confounding variables of age, sex, body mass index, Charlson Comorbidity Index<sup>22</sup>, and American Society of Anesthesiologists class. Allergic reactions were determined with use of an electronic query on administrative data utilizing International Classification of Diseases-9 and 10 codes (see Appendix 2). Following the electronic query, a manual chart review was performed to confirm the presence and type of allergic reaction. Similar to the screening questionnaire, details on the symptoms, timing, and treatment of any allergic reaction were reviewed and graded according to a commonly utilized severity scale proposed by Ring et al.<sup>23,24</sup>: grade 1, skin symptoms and/or mild fever reaction; grade 2, measurable but not life-threatening cardiovascular reaction, gastrointestinal disturbance, or respiratory disturbance; grade

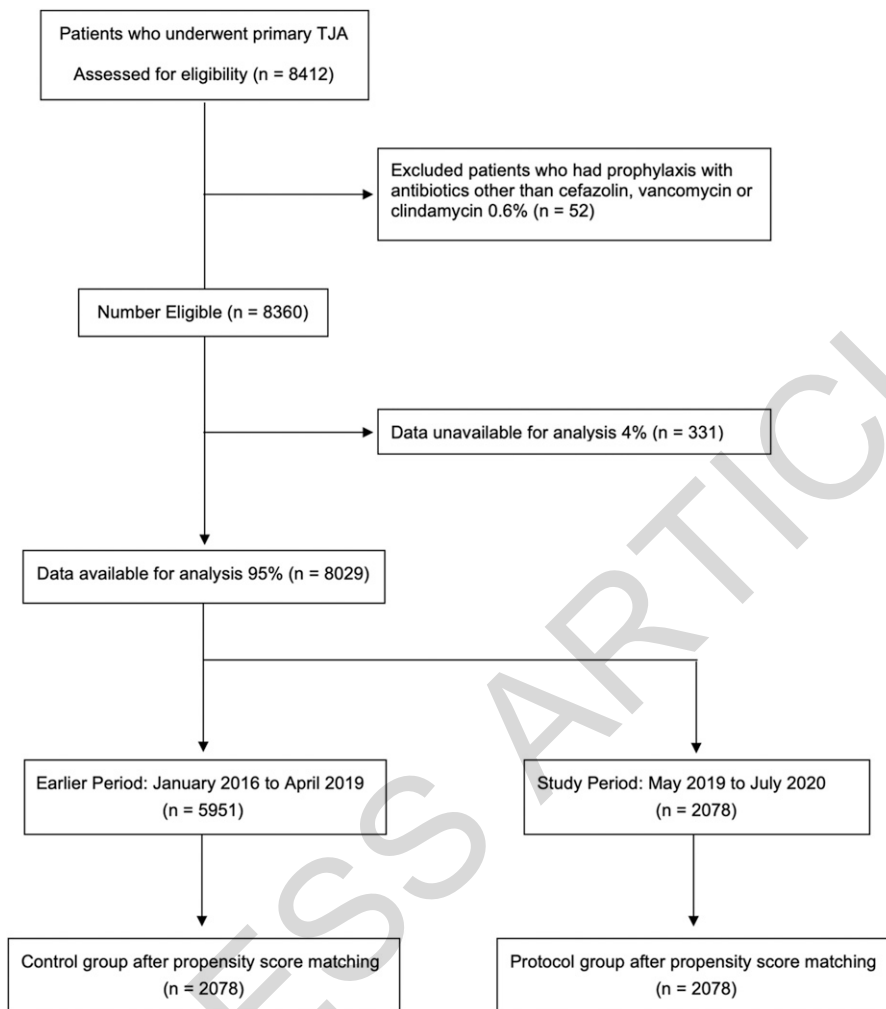


Fig. 1  
Flow diagram outlining the patient selection process.

3, shock and/or life-threatening spasm of smooth muscles; and grade 4, cardiac and/or respiratory arrest. The independent assessor was blinded to the study groups and was not involved in the design of the screening protocol. Primary and secondary outcomes were compared between the 2 groups for a period of 90 days postoperatively.

### Statistical Analyses

A post-hoc power analysis was performed. With a 2-tailed test at 80% power and an alpha of 0.05, a sample size of 1,442 patients would be needed to detect a 5% decrease in non-cephalosporin usage<sup>13,18</sup>. The 2 groups (protocol compared with controls) were matched for age, sex, body mass index, Charlson Comorbidity Index, and American Society of Anesthesiologists class using propensity score matching<sup>25</sup>. Standardized differences for each variable after propensity score matching were <0.1 (see Appendix Fig. 1). Continuous variables were compared with use of a 2-tailed independent t test, whereas categorical variables were compared with use of chi-

square analysis. Significance was set at 0.05. Statistical analyses were performed with use of SPSS (version 20.0; IBM).

### Source of Funding

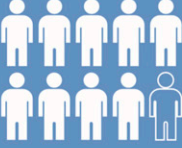
There was no external funding for this study.

### Results

A total of 2,078 patients in the protocol group were matched with 2,078 controls with use of 1:1 propensity score matching (Table I). There were 357 patients (17.2%) in the protocol group who self-reported a penicillin allergy on the screening questionnaire compared with 310 in the control group (14.9%) for whom a penicillin allergy was reported in the electronic health record ( $p = 0.052$ ). The most commonly reported reaction in the protocol group was a non-generalized rash in 133 patients (37.3%) (Table II). There were 118 patients (33.1%) who reported possible allergic or hypersensitivity reactions, including generalized rash or hives ( $n = 84$ , 23.5%), angioedema ( $n = 19$ , 5.3%), and anaphylaxis ( $n = 15$ , 4.2%).

**Did you know that**

 **Penicillin is the most commonly reported drug allergy?<sup>1</sup>**

 **Nine out of 10 patients** reporting a penicillin allergy are not truly allergic<sup>1</sup>

The **CDC joins other experts** in suggesting penicillin allergy evaluation for those who report being allergic to penicillin

**Ask your healthcare provider** about the risk and benefits of penicillin allergy testing and if you are a candidate

**Correctly identifying** those who are not actually penicillin allergic can improve antibiotic prescribing and combat the risk of super-bugs<sup>2</sup>

**What it means for you:**

1. You can safely receive Cefazolin, a less toxic, less expensive and more effective antibiotic for future surgeries and/or hospitalization.

**Next Step After Surgery:**

1. Contact your Primary Care Provider or Allergist to notify them you have been successfully treated with Cefazolin.
2. Ask your provider if you are a candidate for further penicillin allergy testing to confirm you are safe to take other penicillin related antibiotics.

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Fig. 2

Patient handout explaining the low incidence of a true penicillin allergy. CDC = Centers for Disease Control and Prevention.

In total, 1,960 patients (94.3%) in the protocol group received a first-generation cephalosporin, which was significantly higher than the proportion of patients in the control group who received cefazolin before implementation of the protocol ( $n = 1,762$ , 84.8%;  $p < 0.001$ ) (Table III). Multiple logistic regression analysis adjusting for age, sex, body mass

index, Charlson Comorbidity Index, and American Society of Anesthesiologists class showed that patients in the protocol group were 3 times more likely to receive cefazolin (odds ratio [OR], 2.97; 95% confidence interval [CI], 2.38 to 3.71;  $p < 0.001$ ). No other variables were significant in the model (see Appendix 3). No patient in the control group with a penicillin

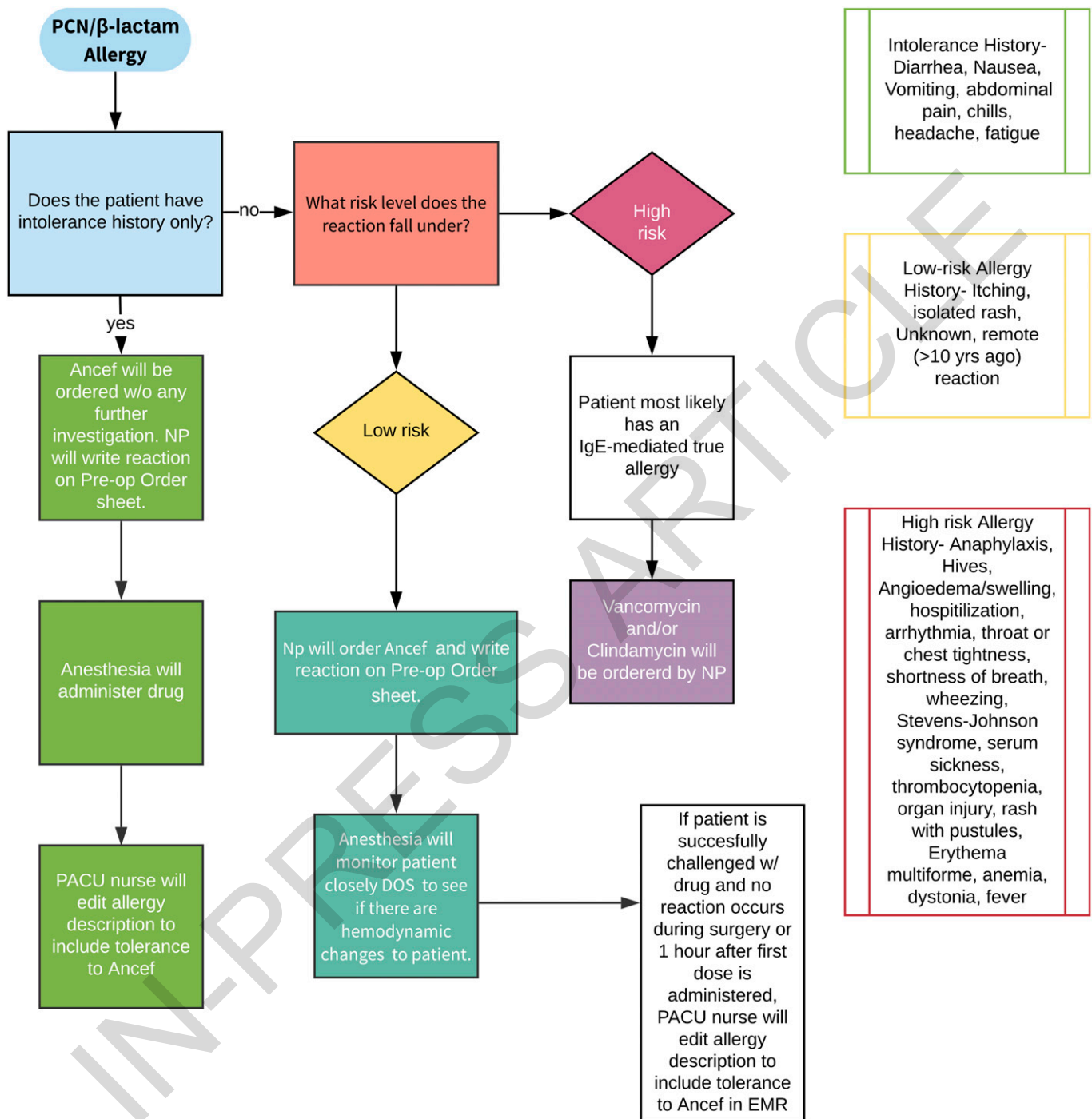


Fig. 3

Risk stratification flow diagram in the screening protocol. PCN = penicillin, NP = nurse practitioner, PACU = post-anesthesia care unit, DOS = day of surgery, and EMR = electronic medical record. Ancef = cefazolin.

allergy label in their electronic health record received a cephalosporin. There was no difference in the rate of adverse reactions to any antibiotic before and after implementation of the screening protocol (0.7% compared with 0.8%, respectively;  $p = 0.857$ ). The majority of allergic reactions that occurred were secondary to cefazolin administration (13 of 15, 86.7% in the control group; 15

of 16, 93.8% in the protocol group). Three of 15 (20.0%) cefazolin allergic reactions occurred in patients with a self-reported penicillin allergy in the protocol group. No patients with an allergic reaction to cefazolin in the control group had a known allergy to penicillin. Of note, all 31 allergic reactions were determined to be immune-mediated and classified as grade 1 (i.e., cutaneous signs

TABLE I Preoperative Patient Characteristics\*

|                           | Control (N = 2,078) | Protocol (N = 2,078) | P Value |
|---------------------------|---------------------|----------------------|---------|
| Age (yr)                  | 64.5 ± 9.4          | 64.4 ± 9.5           | 0.644   |
| Sex                       |                     |                      | 0.433   |
| Females                   | 1,210 (58.2%)       | 1,185 (57.0%)        |         |
| Males                     | 868 (41.8%)         | 893 (43.0%)          |         |
| BMI (kg/m <sup>2</sup> )  | 30.3 ± 5.3          | 30.2 ± 5.5           | 0.639   |
| CCI                       |                     |                      | 0.881   |
| ≤2                        | 2,055 (98.9%)       | 2,056 (98.9%)        |         |
| >2                        | 23 (1.1%)           | 22 (1.1%)            |         |
| ASA class                 |                     |                      | 0.354   |
| I                         | 15 (0.7%)           | 12 (0.6%)            |         |
| II                        | 1,699 (81.8%)       | 1,729 (83.2%)        |         |
| III                       | 358 (17.2%)         | 335 (16.1%)          |         |
| IV                        | 6 (0.2%)            | 2 (0.1%)             |         |
| Procedure                 |                     |                      | 0.314   |
| THA                       | 1,112 (53.6%)       | 1,144 (55.2%)        |         |
| TKA                       | 966 (46.4%)         | 934 (44.8%)          |         |
| Length of stay (day)      | 1.3 ± 0.6           | 1.3 ± 0.6            | 0.798   |
| Penicillin allergy label† | 310 (14.9%)         | 357 (17.2%)          | 0.052   |

\*Values are given as the mean ± standard deviation or as the count with the percentage in parentheses. BMI = body mass index, CCI = Charlson Comorbidity Index, ASA = American Society of Anesthesiologists, THA = total hip arthroplasty. †Either recorded in electronic health records before implementation of the protocol (control group) or self-declared on preadmission questionnaire (protocol group).

only), requiring only antihistamines for treatment. No patients required epinephrine in this study.

In the protocol group, 239 patients (66.9%) were stratified into the low-risk group and given cefazolin despite a self-reported penicillin allergy, including 236 (98.7%) who tolerated the

cefazolin well and 3 who experienced allergic reactions (all grade-1 reactions). These cases resulted in a cross-reactivity rate of 1.3%. No patient had a known cephalosporin allergy prior to the reaction. There were 118 patients (33.1%) in the high-risk group who were given alternative antibiotics, including 1 patient who had a grade-1 reaction following vancomycin administration.

In terms of perioperative adverse events, there was no difference between the control and protocol groups in terms of superficial wound infections (1.2% compared with 0.8%, respectively;  $p = 0.158$ ), deep infections (0.4% compared with 0.5%;  $p = 0.636$ ) or *C. difficile* infections (0.2% compared with 0.1%;  $p = 0.705$ ) (Table IV).

A subgroup of patients (including 38 in the control group and 44 in the protocol group) received vancomycin in addition to cefazolin because of a history or high risk of carriage of methicillin-resistant *Staphylococcus aureus* infection (e.g., nursing home residents and health-care workers). Only 1 superficial infection was recorded in the control group. No patients in this subgroup declared a penicillin allergy preoperatively, and no allergic reactions occurred. Exclusion of this subgroup from the main analysis did not change the findings of the study (see Appendices 4 and 5).

## Discussion

To our knowledge, the present study is the first to evaluate the effectiveness of a simple, protocol-driven screening program to maximize cefazolin usage in patients undergoing

TABLE II Penicillin Allergy Reported in Protocol Group

| Allergy History           | No. (%)     |
|---------------------------|-------------|
| Intolerance history       |             |
| Gastrointestinal upset    | 19 (5.3%)   |
| Unknown history*          | 69 (19.3%)  |
| Low-risk history          |             |
| Non-generalized rash      | 133 (37.3%) |
| Itching                   | 18 (5.0%)   |
| High-risk history         |             |
| Generalized rash or hives | 84 (23.5%)  |
| Angioedema                | 19 (5.3%)   |
| Anaphylaxis               | 15 (4.2%)   |

\*Unknown history refers to an unknown reaction that occurred >10 years ago.

TABLE III Prophylactic Antibiotics Received and Adverse Reactions Recorded\*

|                                  | Control (N = 2,078) | Protocol (N = 2,078) | P Value |
|----------------------------------|---------------------|----------------------|---------|
| Prophylactic antibiotic          |                     |                      | <0.001† |
| Cefazolin‡                       | 1,762 (84.8%)       | 1,960 (94.3%)        |         |
| Vancomycin                       | 290 (14.0%)         | 101 (4.9%)           |         |
| Clindamycin                      | 26 (1.2%)           | 17 (0.8%)            |         |
| Allergic reactions in total      | 15 (0.7%)           | 16 (0.8%)            | 0.857   |
| Allergic reactions by antibiotic |                     |                      | -       |
| Cefazolin                        | 13 (86.7%)          | 15 (93.8%)           |         |
| Vancomycin                       | 1 (6.7%)            | 1 (6.2%)             |         |
| Clindamycin                      | 1 (6.7%)            | 0 (0.0%)             |         |
| Allergic reactions by severity   |                     |                      | -       |
| Grade 1                          | 15 (0.7%)           | 16 (0.8%)            |         |
| Grade 2                          | 0 (0.0%)            | 0 (0.0%)             |         |
| Grade 3                          | 0 (0.0%)            | 0 (0.0%)             |         |
| Grade 4                          | 0 (0.0%)            | 0 (0.0%)             |         |

\*Values are given as the count with the percentage in parentheses. †Significant. ‡Includes a subset of patients in the control (n = 38) and protocol (n = 44) groups who received both cefazolin and vancomycin.

TJA. Implementation of the protocol was associated with a 9% increase in the number of patients who received cefazolin, without a corresponding increase in the rate of allergic reactions. Importantly, two-thirds of patients with a self-reported penicillin allergy were able to receive cefazolin safely without the need for additional consultation or allergy testing.

According to previous studies, <5% of patients labeled with a penicillin allergy have a true IgE-mediated, clinically relevant hypersensitivity reaction<sup>26-28</sup>. This important public-health issue has been highlighted by several authors<sup>2,26</sup>. The present study showed that the incidence of self-reported penicillin allergy was relatively high (17%), consistent with epidemiological studies, with rates of 8% to 20%<sup>29</sup>. When analyzing the specific reactions reported, we found that most patients reported a history of non-generalized rash (37%) or generalized rash as well as hives (23%), which was also in line with previous studies within the orthopaedic literature and other areas of medicine<sup>2,15,30,31</sup>. The consequence of this mislabeling has serious implications because alternatives to cephalosporin have been associated with high rates of periprosthetic joint infection<sup>13</sup>. This concern is further compounded by the threat of antimicrobial resistance, which has reached dangerously high levels globally<sup>32</sup>.

Although the implications of non-cephalosporin antibiotics have been extensively studied<sup>13,15-17</sup>, only a small number of studies have proposed interventions to increase the prescription of beta-lactam agents, and these interventions often include additional consultations and allergy testing<sup>13,18</sup>. Wyles et al. showed that preoperative referral to an allergist allowed the majority of TJA patients to be cleared to receive cefazolin, resulting in an overall cefazolin usage of 95%<sup>13</sup>. Importantly, 11.5% of patients in that study (3,411 of 29,695) had under-

gone preoperative allergy testing. It is imperative to acknowledge the logistical challenges associated with the widespread adoption of this practice, which include increased costs and potential scheduling delays when referring patients to allergists<sup>2</sup>. Blumenthal et al. estimated the cost of a penicillin allergy evaluation to be \$220 per case (range, \$40 to \$537)<sup>19</sup>. By utilizing a simple drug allergy history questionnaire, we were able to adequately risk-stratify patients and provide cefazolin to 94.3% of the cohort. These numbers were similar to the study by Wyles et al. but were achieved without the need for costly and time-consuming tests or consultations.

Safety is perhaps the most important aspect of any screening protocol. The overall incidence of allergic reactions did not increase following implementation of the protocol and was approximately 1% in both groups. Similar to the present study, Kuruvilla et al. implemented a questionnaire-based protocol for antibiotic selection in surgical patients with a penicillin allergy label and found that the percentage of patients who received a cephalosporin increased from 22% to 80% following implementation<sup>33</sup>. Of the 551 patients with a self-reported penicillin allergy who

TABLE IV Adverse Events up to 90 Days Postoperatively\*

|                               | Control (N = 2,078) | Protocol (N = 2,078) | P Value |
|-------------------------------|---------------------|----------------------|---------|
| Superficial infection         | 25 (1.2%)           | 16 (0.8%)            | 0.158   |
| Deep infection                | 8 (0.4%)            | 10 (0.5%)            | 0.636   |
| <i>C. difficile</i> infection | 4 (0.2%)            | 3 (0.1%)             | 0.705   |

\*Values are given as the count with the percentage in parentheses.

received a cephalosporin, no patients required epinephrine and 1 patient had a delayed rash (0.2%). The rate of adverse reactions following penicillin administration reportedly ranges from 0.5% to 2%, with the rate of true IgE-mediated reactions postulated to be even lower<sup>26,34</sup>. In the present study, only 3 patients (1.3%) in the low-risk group had a mild cutaneous reaction, reinforcing the 2% cross-reactivity incidence suggested previously<sup>35,36</sup>. Haslam et al. also retrospectively reviewed 54 TJA patients who reported non-IgE symptoms for their reported penicillin allergy, noting that no patients suffered an adverse reaction after receiving cefazolin<sup>37</sup>. As the R side-chain, rather than the beta-lactam ring, has been found to be the major factor for cross-reactivity<sup>35</sup>, allergy to a penicillin or cephalosporin in a particular generation may not lead to any cross-reactivity with another cephalosporin within the same or different generation if the R side-chains are different (e.g., cefazolin and cephalexin)<sup>38</sup>. Distinctly, cefazolin does not share a similar side-chain with any of the current U.S. Food and Drug Administration-approved beta-lactams, including penicillin<sup>38</sup>, which likely accounts for the low cross-reactivity rate demonstrated in the present study and the literature. As the incidence of cephalosporin allergies in the general population is approximately 2%<sup>39</sup>, it is also possible that the occurrence of an allergic reaction to a cephalosporin in a penicillin-allergic patient is completely coincidental and does not prove causality, especially because there is a threefold increased risk of adverse reactions to unrelated drugs among penicillin-allergic patients<sup>40</sup>. Most importantly, no patients in the cohort had an anaphylactic reaction, likely because of the low incidence of this complication<sup>20,29</sup>. In a large population-based study of 622,456 patients, Macy and Contreras found 13 cases (0.0009%) of physician-documented cephalosporin-associated anaphylaxis<sup>20</sup>. Given the low reliability of allergy self-reporting<sup>6</sup>, historical overestimation of cross-reactivity as a result of contamination of early cephalosporins<sup>7</sup>, and greater understanding of the role of R side-chains in determining cross-reactivity, it is therefore plausible that the relative risk is low. When taken together with the extremely low incidence of severe cephalosporin allergic reactions<sup>20,41</sup>, these data lend support to recent recommendations that cephalosporins can be safely administered in patients with a history of penicillin allergy<sup>35,42</sup>. A simple screening protocol could be utilized as both a safe and effective means to increase the use of first-generation cephalosporins in patients who declare a penicillin allergy. It is possible that allergy testing could be reserved for patients classified as high-risk according to the current protocol, thereby potentially increasing the use of cephalosporins in penicillin-allergic patients.

The present study had several limitations. First, the nonrandomized nature could have introduced selection bias into the study. As the control group consisted of patients who underwent surgery before May 2019 and the protocol group consisted of patients who underwent surgery after May 2019, the difference in time period could have resulted in minor

changes in perioperative management, which could have confounded the analysis of secondary outcomes such as surgical site infection. However, this effect was minimized through the use of a prospective cohort study design with propensity score matching. Second, different methods were utilized to classify a patient as “penicillin-allergic” before and after protocol implementation, with allergy labels being obtained from the electronic health record in the control group and patient-reported in the protocol group. Although the difference in the proportion of patients with an allergy was not significant, the difference in data collection could have upwardly biased the percentage of allergies in the latter group. Nonetheless, we showed that despite a higher prevalence of reported allergies in the protocol group, the number of allergic reactions did not differ significantly. Third, as the incidence of allergic reactions, surgical site infections, and *C. difficile* infections was low, the analysis was underpowered to detect a significant difference in secondary outcomes before and after implementation of the protocol. Finally, as the protocol and questionnaire were designed and implemented at a single institution, it is possible that other institutions with differing patients, providers, and practices may obtain different results following implementation. However, the screening questionnaire was adapted from the American Medical Association Penicillin Allergy Toolkit<sup>21</sup>, which has been widely advocated by the American Medical Association and adopted by multiple institutions in the U.S.<sup>26</sup>, likely increasing the generalizability of our findings.

### Conclusions

Following the adoption of a novel penicillin allergy screening protocol that avoids referrals and additional testing, two-thirds of patients with a self-reported allergy were able to receive cefazolin safely, and the overall rate of cefazolin usage increased by 9%, to 94%, without an increase in adverse reactions. This protocol serves as a simple, free stratification tool that may be utilized to decrease the rate of infection following TJA. ■

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