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2019 John Charnley Award: Increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin

THE VALUE OF ALLERGY TESTING FOR ANTIBIOTIC PROPHYLAXIS

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Aims

The aims of this study were to characterize antibiotic choices for perioperative total knee arthroplasty (TKA) and total hip arthroplasty (THA) prophylaxis, assess antibiotic allergy testing efficacy, and determine rates of prosthetic joint infection (PJI) based on perioperative antibiotic regimen.

Patients and Methods

We evaluated all patients undergoing primary TKA or THA at a single academic institution between January 2004 and May 2017, yielding 29 695 arthroplasties (22 705 patients), with 3411 arthroplasties in 2576 patients (11.5%) having undergone preoperative allergy testing. A series of institutional databases were combined to identify allergy consultation outcomes, perioperative antibiotic regimen, and infection-free survivorship until final follow-up.

Results

Among 2576 allergy-tested patients, 2493 patients (97%) were cleared to use cephalosporins. For the entire cohort, 28 174 arthroplasties (94.9%) received cefazolin and 1521 (5.1%) received non-cefazolin antibiotics. Infection-free survivorship was significantly higher among arthroplasties receiving cefazolin compared with non-cefazolin antibiotics, with 0.06% higher survival free of infection at one month, 0.56% at two months, 0.61% at one year, and 1.19% at ten years ($p < 0.001$). Overall, the risk of PJI was 32% lower in patients treated with cefazolin after adjusting for the American Society of Anesthesiologists (ASA) classification, joint arthroplasty (TKA or THA), and body mass index (BMI; $p < 0.001$). The number needed to treat with cefazolin to prevent one PJI was 164 patients at one year and 84 patients at ten years. Therefore, potentially 6098 PJIs could be prevented by one year and 11 905 by ten years in a cohort of 1 000 000 primary TKA and THA patients.

Conclusion

PJI rates are significantly higher when non-cefazolin antibiotics are used for perioperative TKA and THA prophylaxis, highlighting the positive impact of preoperative antibiotic allergy testing to increase cefazolin usage. Given the low rate of true penicillin allergy positivity, and the readily modifiable risk factor that antibiotic choice provides, we recommend perioperative testing and clearance for all patients presenting with penicillin and cephalosporin allergies.

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First-generation cephalosporins remain the benchmark perioperative antibiotic for total knee arthroplasty (TKA) and total hip arthroplasty (THA). The American Academy of Orthopaedic Surgeons (AAOS) and leading infectious disease authorities, informed by several robust investigations, have recommended that the standard antibiotic prophylaxis for TKA and THA should consist of

1 g to 3 g of cefazolin administered within 60 minutes of surgical incision.[1-10] While cefazolin is specifically recommended by the AAOS, various cephalosporins are preferred regionally across international practice. Cephalosporins are liked for their low side effect profile and excellent coverage across the spectrum of organisms responsible for most prosthetic joint infections (PJIs).[1,2] Furthermore, in addition to direct antimicrobial action, they have been shown to enhance bacterial elimination by the innate immune system beyond their documented *in vitro* efficacy, as measured by laboratory-based bacteriological testing.[11] There are two scenarios where perioperative prophylaxis with cefazolin has been a challenge. The first is in patients with historical or self-reported allergies to antibiotics, most commonly penicillin, that result in changes to perioperative antibiotic selection. Second, patients who are found by screening to be colonized preoperatively with methicillin-resistant *Staphylococcus aureus* (MRSA) represent another patient group where an alternative to cefazolin, typically vancomycin, is often chosen for perioperative prophylaxis. The AAOS recommends use of vancomycin or clindamycin as second-line agents where cephalosporins are thought to be contraindicated.[2]

Although other options to cefazolin are often used for TKA and THA in the setting of reported penicillin allergy, this shift in treatment may not be benign. A recent study of patients undergoing a variety of surgical procedures, including TKA and THA, demonstrated that patients receiving other antibiotics than cefazolin sustained surgical site infections 50% more frequently.[12] Furthermore, while substitutions for cefazolin are frequently recommended to prevent MRSA infection, another prominent report of both surgical and medical patients documented that patients receiving something other than a β-lactam antibiotic due to penicillin allergy had an increased risk of infection with MRSA and *Clostridium difficile*.[13] In an effort to support antibiotic stewardship, there have been calls, including from the American Academy of Allergy, Asthma, and Immunology, to have patients with uncertain or historically documented penicillin allergies undergo formal testing to confirm the presence or absence, as well as the severity, of such an allergy.[14] Efforts have previously been undertaken with antibiotic allergy testing programmes as part of preoperative care pathways for TKA and THA. In 2000, Li et al[15] showed that initiation of antibiotic allergy testing decreased the use of vancomycin in patients with reported penicillin allergies from 30% to 11%. Subsequently, in 2010, Park et al[16] evaluated the safety of perioperative cephalosporin use based on the results of preoperative skin testing for presumed penicillin allergy. The rate of any reaction to the perioperative cephalosporin was 6% in the penicillin skin test positive group compared with 0.7% in the skin test negative group, while the rate of severe reaction was 2% in the skin test positive group *versus* 0.1% in the skin test negative group. These authors concluded that the rate of cross-reactivity between penicillin and cephalosporins is small. However, preoperative testing holds value, as a negative penicillin skin test renders the risk of severe cephalosporin reaction consistent with that of the general population.

Although previous investigations suggest that antibiotic allergy testing may improve care for surgical patients, there is a paucity of literature investigating the effects of prophylaxis choice in a large group of TKA and THA patients. Furthermore, it remains unknown how the perioperative antibiotic regimen impacts on the risk of PJI in this patient population. Therefore, the aims of this study were to: 1) characterize the antibiotic choices for perioperative prophylaxis at the time of primary TKA and THA; 2) assess the efficacy of a preoperative antibiotic allergy testing programme; and 3) determine rates of PJI based on perioperative antibiotic regimen.

Table I. Study demographics by cefazolin usage status (data presented on a per-arthroplasty basis)

Variable	Cefazolin administered (n = 28 174)	No cefazolin (n = 1521)	p-value
Mean age, yrs (SD)	67.1 (11.4)	67.5 (11.2)	0.386*
Sex, n (%)			< 0.001†‡
Female	15 299 (*54.3*)	1053 (*69.2*)	
Male	12 875 (*45.7*)	468 (*30.8*)	
Mean BMI, kg/m² (SD)	31.4 (6.6)	32.7 (7.7)	< 0.001*‡
Arthroplasty, n (%)			0.011†‡
THA	12 068 (*42.8*)	601 (*39.5*)	
TKA	16 106 (*57.2*)	920 (*60.5*)	
Laterality, n (%)			0.958†
Left	13 403 (*47.6*)	722 (*47.5*)	
Right	14 771 (*52.4*)	799 (*52.5*)	
ASA score, n (%)			< 0.001†‡
0	21 (*< 0.1*)	0 (*0.0*)	
1	775 (*2.8*)	19 (*1.2*)	
2	16 265 (*57.7*)	726 (*47.7*)	
3	8989 (*31.9*)	577 (*37.9*)	
4	175 (*0.6*)	13 (*0.9*)	
5	4 (*< 0.1*)	0 (*0.0*)	
N/A	1945 (*6.9*)	186 (*12.2*)	
Known MRSA colonization,§ n (%)	122/2525 (*4.8*)	32/188 (*17.0*)	< 0.001†‡

*Mann–Whitney U test
†Fisher's exact test
‡Statistically significant
§6561 patients underwent *Staphylococcus aureus* testing with 2724 samples undergoing susceptibility testing (i.e. MRSA determination)
BMI, body mass index; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anethesiologists; N/A, not applicable; MRSA, methicillin-resistant *Staphyloccocus aureus*

Patients and Methods

Study population. Following institutional review board approval (study number 18-000888), we used an institutional Total Joint Registry to identify all patients who had undergone primary TKA or THA between January 2004 and May 2017. There was a total of 29 695 arthroplasties (22 705 patients) evaluated, consisting of 17 026 TKAs and 12 669 THAs in the final cohort (Table I). Mean patient age was 67.1 years (SD 11.4; TKA: 68.6 years (SD 9.9); THA: 65.2 years (SD 13.0)); 13 343 of the arthroplasties (44.9%) were performed in male patients and 16 352 (55.1%) in female patients. A total of 5866 patients underwent bilateral arthroplasty (3904 TKA and 1962 THA) over the course of follow-up, with 833 (2.8%; 688 TKA and 145 THA) undergoing simultaneous bilateral surgery.

January 2004 was selected as a starting time for consideration, as this corresponded to the establishment of an institutional

Allergy Testing Registry. Two databases, the Total Joint and Allergy Testing Registries, were subsequently synthesized and combined with multilayer cross-validation, in addition to searches of the electronic medical record, to determine which patients underwent antibiotic allergy testing prior to surgery, as well as outcomes from the allergy consultation, perioperative antibiotic management strategy, and survivorship free of infection until final follow-up. Given the evolving definitions and criteria for postoperative infection, a temporally consistent measure of PJI was provided on the basis of clinical examination and laboratory results deemed consistent with infection (i.e. leading to surgical intervention or antibiotic suppression) on the basis of independent, third-party review of all data by formally trained Total Joint Registry staff. Our Total Joint Registry contacts patients at routine intervals (postoperatively at two years, five years, and every five years thereafter) to screen for complications identified and treated at outside institutions to complement data from internal patient management. PJI is documented as a complication by the third-party reviewers after evaluation of all records if either: 1) the patient has been assigned a diagnosis of PJI by a physician; or 2) the patient has a documented positive culture from an intraoperative or synovial fluid specimen. This set of criteria has been consistently applied since 1988.[17] MRSA colonization status was assessed by querying and documenting preoperative nasal culture results for the entire cohort by employing an institution-wide laboratory data interface to assess MRSA colonization for all patients undergoing preoperative testing (Advanced Cohort Explorer; Mayo Clinic, Rochester, Minnesota).

Statistical analysis. Descriptive statistics were used to present demographic data with means, standard deviations, and percentages, as appropriate. Fisher's exact test was employed for proportions and Mann–Whitney U testing was used for nominal values to compare antibiotic allergy testing as well as antibiotic administration cohorts. Survivorship was investigated using Kaplan–Meier analysis for survival free of PJI. Consequently, univariate and multivariate analysis was performed using Cox proportional hazards regression to evaluate predictors of PJI and account for possible confounders including age, the American Society of Anesthesiologists (ASA) status,[18] and known MRSA colonization. A p-value < 0.05 was considered statistically significant.

Results

Preoperative antibiotic allergy testing was performed in 2576 patients, prior to 3411 arthroplasties (11.5%) on the basis of a patient-provided history of possible penicillin or cephalosporin allergy. Among those tested, 2493 patients (96.8%) and 3310 arthroplasties (97.0%) were cleared by the allergist to use cephalosporins in the perioperative period. Of those arthroplasties with preoperative clearance for cephalosporin administration, 2883 (87.1%) went on to receive cefazolin intraoperatively. For the entire cohort, 28 174 arthroplasties (94.9%) received an operative antibiotic regimen including cefazolin and 1521 (5.1%) received non-cefazolin antibiotics, generally vancomycin or clindamycin. There was no difference in antibiotic cement use between arthroplasties receiving cefazolin (28.7%) and those receiving non-cefazolin antibiotics (30.9%; $p = 0.07$). Of note, positive MRSA colonization testing status was more frequent in arthroplasties receiving non-cefazolin antibiotics (17.0%) compared with patients receiving cefazolin (4.8%; $p < 0.001$; Table I). In addition, ASA class was poorer in the non-cefazolin group (39% of arthroplasties with ASA ≥ 3) than the cefazolin group (33% of arthroplasties with ASA ≥ 3). The inception of preoperative antibiotic allergy testing decreased non-cefazolin use perioperatively from a historical 30% at our institution to 5% in this cohort.

Survivorship free of PJI was significantly higher among arthroplasties receiving cefazolin compared with non-cefazolin antibiotics, with the most rapid divergence occurring within two months of surgery ($p < 0.001$; Fig. 1). Survivorship free of PJI in the cefazolin group compared with the non-cefazolin groups was 99.40% *versus* 99.34% at one month, 99.11% *versus* 98.55% at two months, 98.83% *versus* 98.22% at one year, and 98.15% *versus* 96.96% at ten years (Table II). Cox proportional hazards analysis demonstrated that cefazolin given perioperatively was protective against PJI (hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.45 to 0.68; $p = 0.005$), whereas the following were significantly and positively associated with PJI risk: body mass index (BMI) between 35 kg/m^2 and 45 kg/m^2 (HR 1.73, 95% CI 1.41 to 2.13; $p < 0.001$); BMI > 45 kg/m^2 (HR 3.68, 95% CI 2.73 to 4.97; $p < 0.001$); TKA (HR 1.42, 95% CI 1.18 to 1.71; $p < 0.001$); and ASA class ≥ 3 (HR 1.70, 95% CI 1.42 to 2.03; $p < 0.001$) (Table III). Notably, the increased PJI rate observed in the non-cefazolin group was not attributable to high preoperative MRSA colonization prevalence, as none of the 38 PJIs grew MRSA on culture.

Subsequent multivariable analysis demonstrated that cefazolin administration continued to predict decreased PJI risk (HR 0.68, 95% CI 0.48 to 0.96; $p = 0.027$) even when other predictors of PJI such as BMI, TKA, and ASA were simultaneously considered (Table IV). Multivariable analysis also demonstrated increased risk with the following: BMI between 35 kg/m^2 and 45 kg/m^2 (HR 1.55, 95% CI 1.25 to 1.91; $p < 0.001$); BMI > 45 kg/m^2 (HR 2.90, 95% CI 2.10 to 3.99; $p < 0.001$); TKA (HR 1.32, 95% CI 1.09 to 1.61; $p = 0.005$), and ASA class ≥ 3 (HR 1.44, 95% CI 1.19 to 1.74; $p < 0.001$). The number needed to treat with cefazolin to prevent one PJI was 164 patients at one year and 84 patients at ten years. Therefore, potentially 6098 PJIs could be prevented by one year and 11 905 by ten years in a cohort of 1 000 000 primary TKA and THA patients. Furthermore, when analyzing overall survival (combined septic and aseptic), patients administered cefazolin at the time of surgery demonstrated significantly higher survival with 99.06% one-year survival (95% CI 98.94% to 99.17%), 97.68% five-year survival (95% CI 97.47% to 97.86%), and 96.26% ten-year survival (95% CI 95.96% to 96.55%) as compared with 98.54% (95% CI 97.80% to 99.04%), 96.38% (95% CI 95.17 to 97.30%), and 95.43% (95% CI 93.77% to 96.67%), respectively, in the non-cefazolin group ($p = 0.021$).

Allergy consultation increased the proportion of patients receiving cefazolin by approximately 27.0%, corresponding to 920 additional patients during the study period. Given that cefazolin can be administered immediately prior to incision, whereas vancomycin must be infused for 60 to 120 minutes prior to the start of surgery, the consultation saved a potential

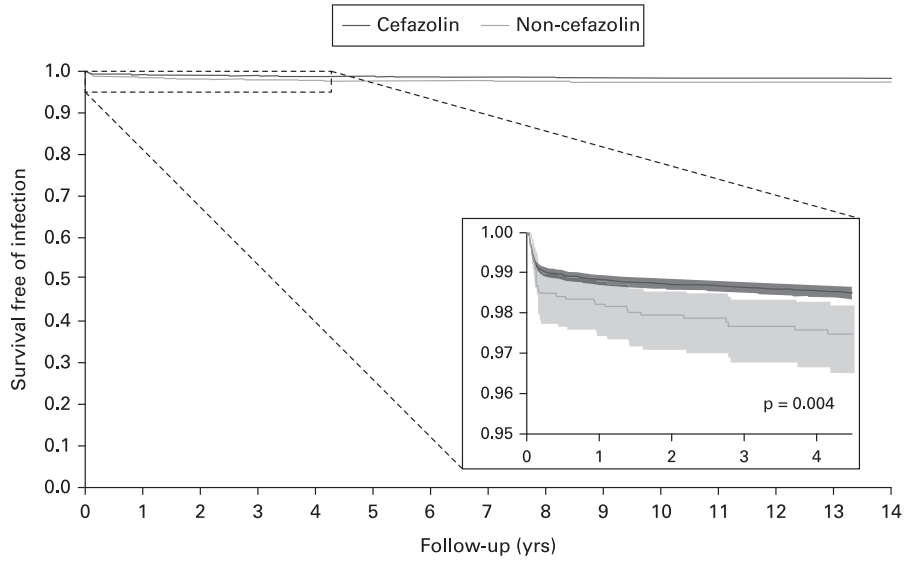

Fig. 1

Survival free of prosthetic joint infection for patients receiving cefazolin (dark grey) and patients receiving non-cefazolin (light grey) antibiotics at the time of primary total knee arthroplasty and total hip arthroplasty. Shaded area represents 95% confidence interval (p = 0.004 between the two groups employing log-rank testing). The most rapid rate of divergence between groups occurred in the first two months after surgery, consistent with an effect related to perioperative antibiotics.

Table II. Infection-free survival by perioperative antibiotic choice following primary total knee arthroplasty and total hip arthroplasty

Perioperative antibiotic	Infection-free survival, %						
	1 mth	2 mths	3 mths	6 mths	1 yr	5 yrs	10 yrs
Cefazolin	*99.40*	*99.11*	*99.02*	*98.95*	*98.83*	*98.46*	*98.15*
Non-cefazolin	*99.34*	*98.55*	*98.49*	*98.42*	*98.22*	*97.44*	*96.96*
Difference	*0.06*	*0.56*	*0.53*	*0.53*	*0.61*	*1.02*	*1.19*

Table III. Univariate Cox proportional hazards analysis for predictors of prosthetic joint infection

Variable	Hazard ratio (95% CI)	p-value
Cefazolin usage		
Non-cefazolin	Reference	
Cefazolin	0.62 (0.45 to 0.86)	0.005*
Age, yrs		
< 55	Reference	
≥ 55	0.82 (0.64 to 1.03)	0.093
Sex		
Female	Reference	
Male	1.07 (0.90 to 1.28)	0.425
BMI, kg/m²		
< 35	Reference	
35 to 45	1.73 (1.41 to 2.13)	< 0.001*
> 45	3.68 (2.73 to 4.97)	< 0.001*
Arthroplasty		
THA	Reference	
TKA	1.42 (1.18 to 1.71)	< 0.001*
ASA score		
< 3	Reference	
≥ 3	1.70 (1.42 to 2.03)	< 0.001*
Known MRSA colonization		
No	Reference	
Yes	2.19 (0.90 to 5.32)	0.085

*Statistically significant

CI, confidence interval; BMI, body mass index; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, the American Society of Anesthesiologists; MRSA, methicillin-resistant *Staphylococcus aureus*

921 to 1842 hours of preoperative holding time during the study period. Based on data regarding cefazolin superiority in preventing PJI and published charges for TKA and THA PJI treatment, allergy consultation prevented between $976 494 and $1 141 006 of direct complication-related in-hospital charges, not including outpatient costs, loss of work, and the above calculated preoperative holding time.

Discussion

PJI is one of the most feared complications following TKA and THA. In an effort to decrease PJI, perioperative antibiotics are routinely administered to mitigate risk, with cefazolin remaining the standard protocol. However, other options to cefazolin are often used for patients with previously documented penicillin allergies due to concern about cross-reactivity and presumed equivalent efficacy. Newly emerging anxiety regarding this practice stems from low rates of penicillin allergy upon formal testing in combination with the decreased antibiotic efficacy observed with options such as vancomycin and clindamycin. As such, this study aimed to evaluate the impact of a formal preoperative care pathway for antibiotic allergy testing prior to TKA and THA and to assess risk modulation of PJI based on a perioperative antibiotic regimen. This large cohort study demonstrates that an antibiotic allergy testing programme is both an effective means to increase cefazolin use, and also that cefazolin administration decreases PJI risk, even after controlling for potentially confounding comorbidities such as BMI and ASA score.

Table IV. Multivariable Cox proportional hazards analysis for predictors of prosthetic joint infection

Variable	Hazard ratio (95% CI)	p-value	Modifiable
Cefazolin usage			Yes
Non-cefazolin	Reference		
Cefazolin	0.68 (0.48 to 0.96)	0.027*	
BMI, kg/m²			Possibly
< 35	Reference		
35 to 45	1.55 (1.25 to 1.91)	< 0.001*	
≥ 45	2.90 (2.10 to 3.99)	< 0.001*	
Arthroplasty			No
THA	Reference		
TKA	1.32 (1.09 to 1.61)	0.005*	
ASA score			No
< 3	Reference		
≥ 3	1.44 (1.19 to 1.74)	< 0.001*	

*Statistically significant

CI, confidence interval; BMI, body mass index; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists

Preoperative antibiotic allergy testing is recommended as an important part of antibiotic stewardship by the American Academy of Allergy, Asthma, and Immunology for all surgical patients with a self-reported or uncertain penicillin allergy.[14] Many authors have concluded that penicillin allergy is overdiagnosed, leading to excess economic strain on the healthcare system and inappropriate care for patients.[19] Furthermore, even in circumstances where patients have sustained proven reactions to penicillin in the past, recent research suggests these sensitivities may not be permanent. Over time, the antibodies may clear as the immune system matures, with many patients becoming skin test negative after a ten-year interval.[20] In addition, it has been shown that patients with penicillin allergy who receive an alternative to cephalosporins are at increased risk for surgical site infections, including MRSA.[12,13] Therefore, it seems apparent that every effort should be made to ensure patients are evaluated for antibiotic allergies that may alter their perioperative regimen.

Li et al[15] reported early results of a preoperative penicillin allergy testing programme in TKA and THA patients, showing a decrease in vancomycin use from 30% to 11%. The impetus for this quality improvement project was to decrease formation of resistance to vancomycin. Park et al[21] built on the initiation of this same programme to evaluate safety of cephalosporin use in surgical patients based on penicillin skin test results. In 2006, they demonstrated that only 0.7% of patients with a negative penicillin skin test who received cefazolin went on to have some form of reaction. In 2010, the group demonstrated the rate of any reaction to cephalosporins was 6% in the skin test positive group compared with 0.7% in the skin test negative group and 2% *versus* 0.1% with respect to severe reactions.[16] Collectively, these studies showed the positive impact of a preoperative antibiotic allergy testing programme and confirmed the safety of using cephalosporins in patients with negative penicillin skin tests. Our current study builds on this work in a much larger cohort of patients specifically undergoing TKA or THA. We found that 97.0% of tested patients were cleared to use cephalosporins, with 87.1% of tested patients eventually receiving cefazolin intraoperatively. This drastically decreased use of alternative agents. However, approximately 10% of tested patients that were cleared still did not receive cefazolin. This was primarily due to MRSA colonization, in which case options such as vancomycin were used. However, vancomycin as a monotherapy in these circumstances may not represent optimal management as studies have shown cefazolin and vancomycin act synergistically against MRSA and, additionally, vancomycin exhibits relatively poor coverage against the wider spectrum of bacteria responsible for PJI.[1,5,6] Consequently, it may be prudent for surgeons to consider dual administration of cefazolin and vancomycin in cases of known MRSA colonization.

There are situations where preoperative antibiotic allergy testing is logistically challenging or results obtained are indeterminate. This creates a conundrum for the care team, typically resulting in use of an alternation to cephalosporins. However, anaesthetists have recently suggested that test dosing of cefazolin be performed in the operating room for patients with an unclear tolerance to this medication.[22] The rationale for this is simple; testing a patient for an extremely rare, but potentially severe, reaction can be safely accomplished in the anaesthetic suite. If the test dose is well-tolerated, the patient can receive optimal antibiotic management and have the allergy removed from their record for future care.

The current study demonstrates a significantly decreased risk of PJI with the use of cefazolin compared with other options, such as vancomycin and clindamycin, for perioperative TKA and THA prophylaxis. While this has previously been suggested in heterogeneous surgical populations,[12,13] this is the first study to our knowledge documenting this difference in a well-powered cohort of TKA and THA patients. The most rapid divergence in PJI rate between groups occurred in the first two months after surgery, lending credence to the relationship with perioperative care and antibiotic choice.

Various factors were evaluated that could potentially confound our observed results. To this end, variables such as ASA class, MRSA status, and BMI were evaluated between groups and controlled for using multivariable methods when shown to be predictive of PJI outcome. We believe that this is important given that patients with more comorbidity have clearly demonstrated higher risk for infection and BMI is a well-documented risk factor for PJI in TKA and THA.[23,24]

Multivariable analysis evaluating the effect of perioperative antibiotics while simultaneously controlling for BMI and ASA classification demonstrated that cefazolin administration maintained a significant relationship with PJI risk. A crucial application of this finding relates to the degree to which these elements are modifiable (Table III). We propose that antibiotic choice is largely modifiable, especially in light of the high rate of clearance observed in our Allergy Testing Registry. In contrast, BMI is potentially modifiable, but the literature has shown this is difficult for most patients and surgeons to achieve.[23,24] Furthermore, a drastic change in BMI puts patients at risk of becoming nutritionally deficient, thus exchanging one PJI risk factor for another.[25] Finally, ASA classification encompasses the patient's age and comorbidity burden, which may be perioperatively optimized, but is hard, if not impossible, to modify in a meaningful way.

This study must be interpreted in light of important limitations. First, this is a retrospective cohort study of patients that did not have rigid criteria applied to the ultimate choice of perioperative antibiotic prophylaxis. As such, it is difficult to control for factors such as variation in surgeon practice, logistical challenges to clearing certain patients for cefazolin use, and characteristics that may be associated with both a need for non-cefazolin agents and an increased baseline risk for PJI. Nevertheless, these weaknesses were mitigated by the large cohort sample size and validated internal registries, which enabled detailed assessment of potential confounding factors. Even after controlling for important known variables, the relationship of increased PJI risk with use of non-cefazolin antibiotics remained strongly associated. Second, causative organism and susceptibilities are not known for all the cases of PJI reported in this cohort. This is due to some aspirations being culture-negative, while other PJIs were identified and treated at outside institutions. However, this did not compromise our definition of PJI, as we classified patients with laboratory results and clinical examination consistent with PJI that were treated with either surgery or antibiotic suppression. Third, we are unable to identify the timing of administration for these antibiotics. Cefazolin is recommended to be given within 60 minutes of incision, whereas vancomycin is recommended between 60 and 120 minutes prior to incision. It is possible that timing of administration may impact efficacy. In cases where vancomycin must be used and there is a delay in administration, intraosseous routes can be considered.[26,27] Lastly, we recognize that various cephalosporins are preferred as first-line agents for antimicrobial prophylaxis across practices internationally. Cefazolin is the preferred agent by the AAOS and at our institution. Therefore, it is the only cephalosporin we were able to evaluate in this study. Based on known coverage spectrums, it is likely that results are similar between different cephalosporins; however, this needs to be validated by further study.

Our investigation demonstrates a significantly lower rate of PJI when cefazolin is used for prophylaxis during primary TKA and THA, which is likely to be attributable to the superior spectrum of coverage for common PJI organisms afforded by cefazolin compared with vancomycin or clindamycin. This work also highlights the positive impact of a formal preoperative antibiotic allergy testing programme, which effectively increased cefazolin usage to over 80% of patients tested. Given the low rate of true penicillin allergy positivity and readily modifiable risk factor that antibiotic choice provides, we recommend perioperative testing and clearance for all patients presenting with penicillin and cephalosporin allergies.

Take home message

- Prosthetic joint infection rates are increased with the use of non-cefazolin antibiotics following primary total knee arthroplasty and total hip arthroplasty.
- Preoperative antibiotic allergy testing is an effective method to increase safe cefazolin usage.
- We recommend testing all patients with a history of penicillin allergy preoperatively, and suggest that cefazolin should be used preferentially in all cases when deemed safe by the surgical team. This includes dual prophylaxis with cefazolin and an agent such as vancomycin for patients that are colonized with methicillin-resistant *Staphylococcus aureus* (MRSA).

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