

Perioperative Clindamycin Use in Penicillin Allergic Patients Is Associated With a Higher Risk of Infection After Shoulder Arthroplasty

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Abstract

Background: This study determines whether infection rates differ between prophylactic antibiotic use for patients with or without penicillin allergy before shoulder arthroplasty surgery.

Methods: Seven thousand one hundred forty primary shoulder arthroplasties operated between 2005 and 2016 were identified. We compared deep surgical site infection risk of patients who received perioperative vancomycin alone (6.2%, N = 444) or clindamycin alone (7.1%, N = 508) for penicillin allergy versus patients who received cefazolin alone without penicillin allergy (86.7%, N = 6,188).

Results: Seventy deep infections (1.2% 5-year cumulative incidence) were observed. The most common organism was *Cutibacterium acnes* (39.4%, N = 27). Compared with patients treated with cefazolin, infection risk was not different for those treated with vancomycin (hazard ratio = 1.17, 95% confidence interval 0.42 to 3.30, $P = 0.8$), but a higher risk of infection was identified for those treated with clindamycin alone (hazard ratio = 3.45, 95% confidence interval 1.84 to 6.47, $P < 0.001$).

Conclusion: A higher risk of postoperative infection is found after prophylactic use of intravenous clindamycin antibiotic after shoulder arthroplasty. Vancomycin is preferred over clindamycin for patients with penicillin allergy.

Level of Evidence: III, retrospective cohort study

The incidence of shoulder arthroplasty (SA) has increased notably over the past decade.¹ Despite advancements in implant design, technique, and surgeon prophylaxis methods, infection rates have not declined and continue to be a devastating issue.¹ Infection rates for SA have been reported between 0% and 5%.^{2,3} Previous studies show infection eradication only in 63% of patients with 68% unsatisfactory results.³ Furthermore, postoperative infection

is an expensive issue for healthcare systems and may be compounded by future changes in reimbursement.¹

Many principles of infection prevention after SA have been applied from lower extremity arthroplasty studies.⁴ However, diagnostic and therapeutic considerations differ between SA and lower extremity arthroplasties because of differences in anatomy, surgical technique, surgical volume, and native skin and deeper tissue organism prevalence. Identifying factors that are

unique to SA is therefore important. In particular, indolent subclinical periprosthetic joint infection (PJI) with *Cutibacterium acnes* is the most common presentation for infection after SA, which is in part because of its unique role as host flora around and within the shoulder anatomy.⁵ This presentation contrasts with a more acute presentation of lower extremity PJI in which other organisms are more commonly isolated.

Large-scale studies examining patient risk factors for PJI after SA are sparse, and fewer have looked at prophylaxis measures modifiable by the surgeon.^{6,7} Current guidelines recommend cefazolin to be infused to patients before surgical incision as an infection prophylaxis method.⁸ However, for patients allergic to penicillin, or cephalosporins, other antibiotics including vancomycin or clindamycin may be administered to avoid an allergic reaction. These antibiotics have different biochemical properties, and their efficacy might vary depending on factors including organism prevalence and changing organism profiles.

We sought to assess deep surgical site infection (SSI) risk of patients who received perioperative intravenous (IV) vancomycin or clindamycin antibiotic compared with patients who received cefazolin prophylaxis.

Methods

Data Source

A cohort study was conducted using data from the organization's integrated healthcare system's Shoulder Arthroplasty Registry.⁹ This registry was established in 2009 in a large healthcare system that has more than 12.2 million members throughout the United States. Healthcare plan

membership has previously been shown to be demographically representative of the geographical areas in which it covers.¹⁰ This registry collects information such as procedures performed, surgical indications, patients, and implants using electronic intraoperative forms completed at the point of care by the operating surgeons and then supplemented using electronic health records and administrative claims. A detailed summary has been published previously.^{9,11,12} Surgical outcomes were prospectively monitored using electronic screening algorithms and were validated both by trained clinical content experts and the study authors. The registry captured 100% of procedures.

Inclusion and Exclusion Criteria

The study sample included all primary shoulder arthroplasties, performed between 2005 and 2016 in Hawaii, Northern California, Northwest Pacific Region, and Southern California. To maximize data integrity, procedures performed in contract facilities that had no detailed intraoperative medication data such as antibiotic use were not included. Patients who received simultaneous or staged bilateral procedures were considered to have two shoulder arthroplasties. The final sample included shoulder arthroplasties from 297 surgeons and 39 hospitals.

Exposure of Interest

We compared the following three treatment groups based on their penicillin-family allergy and antibiotic type received: (1) patients who received vancomycin alone for penicillin allergy, (2) patients who received clindamycin alone for penicillin allergy, and (3) patients without allergy who

received cefazolin alone. Information about specific antibiotic use was obtained from the medication administrative record module, and drug allergies were from patients' clinical system records using the electronic health record. Patients with penicillin-family allergy were defined as those who reported allergic reactions to penicillin and cephalosporins. Patients with unavailable antibiotic information (N = 9) were excluded. To minimize indication bias of high-risk cases, patients who received multiple antibiotics were not studied.

Deep Infection

The main outcome was deep post-surgical infection. Owing to variability in its clinical presentation of PJI and the lack of strong evidence differentiating the role of *C. acnes* as a host and/or pathogen, no widely accepted definition is found for PJI of the shoulder.¹³ Although several classifications have recently been developed, their clinical applicability has not been validated.^{14,15} This study used a composite outcome for infection including a diagnosis of deep SSI and/or revision surgery due to infection. Data are continuously monitored by the organizational registry until health insurance membership termination or death. Infections were identified using a comprehensive electronic screening algorithm of electronic medical records and administrative claims of the institution using *International Classification of Disease, Clinical Modification, Ninth Revision (ICD-CM-9)*.^{11,12} The screening algorithm had a 97.8% sensitivity and 91.5% specificity. After initial electronic review, all cases flagged by the electronic screening are adjudicated by a trained clinical content expert using modified National

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Healthcare Safety Network/Centers for Disease Control and Prevention guidelines.¹⁶ Infections were also identified by the reason for revision surgery and supported clinically by more than one of the following criteria: purulent drainage from the deep incision, fever, localized pain or tenderness, a positive deep culture, and/or a diagnosis of deep infection by the operating surgeon based on intraoperative findings.

Infecting Organisms

All infection cases were supplemented with infecting organisms' information from tissue-cultured microbiology reports. In addition to all-cause infection, we analyzed infection caused by *C acnes* alone because of its high prevalence similar to shoulder skin flora.

Confounders

Patient- and procedure-specific risk factors for deep infection identified in the same cohort in a previous study were included as potential confounders, including age (<60 versus 60+ years), sex (male versus female), procedures (reverse total SA versus total SA, hemiarthroplasty, and humeral head arthroplasty), and indication (trauma versus elective).⁶ Additional covariates such as body mass index (30 to 35, >35 versus <30), American Society of Anesthesia classification (3+ versus 1 to 2), diabetes (yes versus no), antibiotic cement (yes versus no), and antibiotic irrigation (yes versus no) were also included in the final model as potential confounders.^{17,18}

Statistical Analysis

Infection was modeled as a time-to-event outcome using mixed-effect Cox proportional hazard regression with random intercepts at the surgeon level and hospital level, and *C acnes*-specific infection was modeled

as competing risk using Fine-Gray proportional hazard regression of subdistribution with a clustering effect at the surgeon level. All models included exposure and all potential confounders listed above as fixed effect. To account for correlated failure times within the same surgeon or hospital due to risk factors that were difficult to measure but important to account for, such as surgeon experience, challenging cases received, hospital protocol, facility-installed device, MRSA outbreak, etc., we modeled these with random intercepts and relaxed the linear assumption of any measurable surrogate.

The proportional hazard assumption for the exposure variables was checked by plotting the Schoenfeld residuals against the vector of unique failure times. The assumption was met, implying that the factors investigated have a constant effect on the hazard over time. A statistical power of over 80% was achieved to detect a hazard ratio (HR) of 2 or greater, based on an overall incidence rate of 0.27 events per 100 person-years.

To account for missing values, fully conditional specification multiple imputations using the Markov chain Monte Carlo estimation method were performed to create 50 versions of the analytic data set. Each data set was separately analyzed using the same model, and the results were combined using Rubin's rules. The imputation model included all variables and the Nelson-Aalen estimator of the cumulative baseline hazard at the survival time.¹⁹ Analyses were performed using R version 3.3.0. $P < 0.05$ was the statistical significance threshold used for this study, and all tests were two-sided.

Results

The study consisted of 7140 primary SA procedures, of which 6.2% (N = 444) received vancomycin for

penicillin-family allergy, 7.1% (N = 508) received clindamycin for penicillin-family allergy, and 86.7% (N = 6,188) without penicillin-family allergy received cefazolin. The study sample comprised mostly women (55.5%) with age of at least 60 years (84.9%) (Table 1).

During the follow-up period, 70 all-cause infections (1.2% 5-year cumulative proportion) were observed. Twenty-seven of them (0.5% 5-year cumulative proportion) were infected by *C acnes* (Table 2), which was also the most common infecting organisms (38.6%, 27/70) (Table 3).

Compared with patients who received perioperative cefazolin without penicillin-family allergy, a higher infection risk was observed in patients who received clindamycin (HR = 3.45, 95% confidence intervals [CIs] 1.84 to 6.47, $P < 0.001$), but no difference in infection risk was observed in those received vancomycin (HR = 1.17, 95% CI 0.42 to 3.30, $P = 0.760$) (Table 2).

For *C acnes* as an infecting organism of interest, an elevated risk continued to be found for patients who received perioperative clindamycin (HR = 4.04, 95% CI 1.25 to 13.06, $P = 0.019$), but not for those who received vancomycin (HR = 0.85, 95% CI 0.15 to 4.90, $P = 0.858$), compared with patients who received cefazolin (Table 2).

Discussion

Analyzing common prophylaxis methods is important to determine effective and cost-effective strategies for preventing postoperative infection. Previous studies of lower extremity arthroplasties suggest that perioperative antibiotic selection may affect infection risk.²⁰⁻²² Identification of less effective antibiotics and patterns of antibiotic susceptibilities can optimize prophylaxis effectiveness and reduce the risk of

Table 1

Baseline Characteristics of Patients Underwent Shoulder Arthroplasty, 2005-2016				
Factor	Cefazolin, N = 6,188	Vancomycin, N = 444	Clindamycin, N = 508	Total, N = 7140
Age (yr): 60+	84.5% (5,229)	87.4% (388)	87.6% (445)	84.9% (6,062)
Female	53.7% (3,323)	67.6% (300)	66.9% (340)	55.5% (3,963)
RTSA	22.4% (1,385)	31.3% (139)	29.3% (149)	23.4% (1,673)
Trauma	15.5% (962)	14.2% (63)	13.0% (66)	15.3% (1,091)
BMI				
<30	55.7% (3,040)	54.8% (210)	51.9% (233)	55.4% (3,483)
30-35	25.1% (1,372)	24.8% (95)	22.9% (103)	25.0% (1,570)
35+	19.2% (1,046)	20.4% (78)	25.2% (113)	19.7% (1,237)
ASA: 3+	45.4% (2,666)	57.0% (243)	51.1% (247)	46.6% (3,156)
Diabetes	27.7% (1,717)	27.9% (124)	32.9% (167)	28.1% (2,008)
Antibiotic cement	15.3% (945)	13.5% (60)	14.2% (72)	15.1% (1,077)
Antibiotic irrigation	25.4% (1,571)	8.8% (39)	34.1% (173)	25.0% (1,783)

ASA = American Society of Anesthesia classification, BMI = body mass index, RTSA = reverse total shoulder arthroplasty
Missing: age N = 3 (<1%), sex N = 4 (<1%), BMI N = 850 (11.9%), and ASA N = 364 (5.1%).

Table 2**Number of All-Cause Infection and *C acnes*-specific Infection by Antibiotics Administered at Shoulder Arthroplasty, N = 7,140**

Antibiotics	All-Cause			<i>C acnes</i>		
	N (%)	HR (95% CI)^a	P	N (%)	HR (95% CI)^a	P
Cefazolin	53 (1.0)	1.00 (reference)	—	21 (0.4)	1.00 (reference)	—
Vancomycin	4 (1.1)	1.17 (0.42 to 3.30)	0.760	1 (0.3)	0.85 (0.15 to 4.90)	0.858
Clindamycin	13 (3.2)	3.45 (1.84-6.47)	<0.001	5 (1.3)	4.04 (1.25-13.06)	0.019
Overall	70 (1.2)	—	—	27 (0.5)	—	—

CI = confidence interval, HR = hazard ratio

^a Adjusted for patient, surgical, surgeon, and hospital risk factors.

N = number of infections observed, % = 5-year incidence proportion, Kaplan-Meier estimation.

organism resistance. However, a lack of studies specific to SA that examine these infection prevention measures exists.

Our study found a markedly higher risk of SSI with IV clindamycin prophylaxis compared with first-line antibiotic cefazolin administration. A 3.5 times higher overall infection risk was found when perioperative IV clindamycin was used compared with cefazolin. Furthermore, this condition was seen to extend with *C acnes* infection risk. An increased risk has also been shown with other types of surgeries where gram-positive organisms were shown to be resistant

in vitro to clindamycin.²³ Robertsson et al²¹ analyzed the Swedish Knee Arthroplasty Register and reported 1.5 times higher risk of SSI when clindamycin was used compared with a third-generation cephalosporin such as cefazolin. Clindamycin was also reported to have a four times higher risk of SSI compared with cephalosporins as a prophylactic antibiotic for soft-tissue transfers in head and neck surgery.²⁴

Although clindamycin is a bacteriostatic agent, cefazolin carries a bactericidal action against organisms. Changing organism profiles and antibiotic resistance may play a role

for its decreased effectiveness. One study reported a susceptibility rate for methicillin-resistant *Staphylococcus aureus* in tertiary care centers to be 99.9% for vancomycin and only 48% for clindamycin.²⁵ Another study analyzed current regional and state antibiograms and found markedly decreased susceptibilities to clindamycin to multiple organisms including MSSA and central nervous system.²⁶

Differentiating the role of *C acnes* within the shoulder as either a host or pathogen remains to be determined. In previous studies analyzing PJI, *C acnes* accounted for between

26 and 69% positive cultures,^{27,28} which is consistent with our study in which *C acnes* made up 39% of cultured organisms. Therapeutic measures targeting *C acnes* once it is identified as a pathogen can improve clinical outcomes. However, these treatments may change over time with an adapting organism resistance profile. Earlier studies beginning in 2010 revealed little resistance to clindamycin antibiotics.²⁹ Subsequent reports have shown an increase in clindamycin resistance from positive *C acnes* isolates up to 22% of the time.³⁰ One study also reported a high incidence of PJI with *C acnes* (comprising 72% of positive cultures) after implantation of a specific SA implant,³¹ which may partly be related to their preoperative antibiotic protocol that administered clindamycin alone if the patient was penicillin allergic. Patients may overreport penicillin allergy, and more than 90% of those patients can tolerate first-line cephalosporins. Only a small fraction of these patients will have cross-reactivity with cephalosporin medications.³² Furthermore, in penicillin allergic patients, some surgeons may choose clindamycin prophylaxis because of concerns for possible *C acnes* infection specific to the shoulder. One study of shoulder fellowship-trained surgeons showed it was the third most commonly prescribed perioperative antibiotic.³³ Rao et al³⁴ showed that using specific IV antibiotic prophylaxis to cover *C acnes* did not reduce positive tissue culture burden after administration, thus supporting our clinical findings. Similar to Robertsson et al,²¹ we recommend investigation into the severity of the patient's reported penicillin allergy symptoms and anesthesia-controlled test dose administration of first-line prophylaxis antibiotics such as cefazolin before use of second-line antibiotic prophylaxis. Further prospective investigations are

Table 3

Infecting Organisms (N = 70)	
Infecting Organisms	Infections, N = 70
<i>C acnes</i>	28.6% (20)
<i>C acnes</i> , MSSA	1.4% (1)
<i>C acnes</i> , <i>S aureus</i>	1.4% (1)
<i>C acnes</i> , Staph Coag Neg	5.7% (4)
<i>C acnes</i> , gram + cocci	1.4% (1)
<i>Enterobacter aerogenes</i>	1.4% (1)
<i>Enterobacter cloacae</i>	5.7% (4)
Gram + cocci	1.4% (1)
Gram + cocci, <i>S aureus</i>	1.4% (1)
Gram + cocci, <i>S epidermidis</i>	2.9% (2)
Gram + rods, <i>C acnes</i>	1.4% (1)
MRSA	2.9% (2)
MSSA	4.3% (3)
<i>Proteus mirabilis</i>	1.4% (1)
<i>Pseudomonas aeruginosa</i>	1.4% (1)
<i>Pseudomonas aeruginosa</i> , <i>Morganella morganii</i>	1.4% (1)
<i>S aureus</i>	2.9% (2)
Staph Coag Neg	5.7% (4)
Staph Coag Neg, <i>Streptococcus</i>	1.4% (1)
<i>S epidermidis</i>	1.4% (1)
Cultures—but diagnosis+	24.3% (17)
MSSA = methicillin-sensitive <i>Staphylococcus aureus</i> , MRSA = methicillin-resistant <i>Staphylococcus aureus</i> .	

needed to identify safe and effective ancillary antibiotic administration practices.

We did not find a difference in benefit with perioperative IV antibiotic use of vancomycin compared with cefazolin antibiotics. A recent study analyzing hip and knee arthroplasties with general surgery and cardiac surgeries found a 50% increased odds of SSI which they attributed to using second-line antibiotics, with more receiving clindamycin compared with vancomycin.²⁰ Kheir et al³⁵ reported that many lower extremity arthroplasty patients receiving vancomycin prophylaxis were underdosed at their institution, and patients receiving vancomycin had a 58% increased risk of infection compared with those patients receiving cefazolin prophylaxis. Others have reported that IV vancomycin antibiotics in

lower extremity arthroplasty procedures did not affect SSI risk after its use and advocated large database and registry studies to further study its relationship.²² We did not find a notable risk difference when using vancomycin prophylaxis compared with cefazolin, possibly because of a uniform set of electronic medical record order sets within our health-care system that optimizes appropriate pharmaceutical dosing based on weight. Based on this data set, for those who need to avoid cephalosporins or penicillin, vancomycin might be a better perioperative antibiotic choice compared with clindamycin.

Challenges in optimizing the ability to obtain all true-positive cultures with PJI of the shoulder remain. Despite clear positive preoperative and intraoperative findings for infection,

some cultures may remain negative. By contrast, indolent organisms native to the skin and deeper layers can lead to false-positive results.³⁶ We included all positive cultures with preoperative findings consistent with infection and negative cultures with positive surgeon findings for infection. Our negative culture incidence of 24% is consistent with past studies, which have reported rates between 13% and 44%.^{27,37} This fact may be partly explained by standardization of the regional laboratory culture media incubation time to 14 days during the early part of the study period.

Strengths of the study include 100% collection and validation of prospective data from a multicenter SA registry and the large, representative sample of patients, surgeons, and hospitals from an integrated nationwide healthcare system. In addition, this registry's data contain greater detail on the cohort, surgical indication, and procedures than typical surgical databases, which may rely only on administrative data with limited validation mechanisms. This registry longitudinally maintains and validates outcome data, therefore minimizing information bias. The cohort of this healthcare system has been shown to be socioeconomically and demographically representative of the geographical area it covers, making our findings generalizable to other patients in the region.¹⁰ Given the rarity of deep infection and short Centers for Disease Control and Prevention surveillance guideline, an observational study such as this one with active ongoing surveillance is essential because it identifies indolent infection after the surgery. Regarding the outcome capture rate, our registry implemented rigorous quality control and data validation processes with 97.8% sensitivity and 91.5% specificity at initial screening,¹¹ which makes the data more reliable than repository databases that are subject to underreported

events and reporting bias of severe cases. The healthcare system also includes a centralized microbiology laboratory with a standardized protocol for specimen processing.

This study had several limitations. First, the registry does not capture information for patients who are terminated from the healthcare plan. The overall rate of termination from healthcare plan was 7% (3% in the clindamycin group, versus 5% to 7% in the vancomycin and cefazolin groups). Second, the interaction of multiple concurrent antibiotics could not be evaluated because of the low amount of overall infection events. To reduce the influence of indication or selection bias, we purposefully excluded those patients receiving multiple perioperative antibiotics. Vancomycin or clindamycin groups were only included from penicillin allergy patients to further control for selection bias. We observed a nearly equal distribution in frequency among perioperative use of clindamycin and vancomycin for penicillin allergy patients (47%:53%). Finally, other antibiotic prophylaxis used in bone cement or tissue irrigation may influence infection risk. These factors were controlled in our multivariable analysis, to account for patient, hospital, and surgeon differences.

Conclusion

Surgeon selection of perioperative IV antibiotic can affect infection risk after primary SA. A higher risk of postoperative infection is found after prophylactic use of IV clindamycin antibiotic compared with cefazolin. Vancomycin is preferred over clindamycin for patients with penicillin allergy.

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