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Perioperative Antibiotic Prophylaxis Has No Effect on Time to Positivity and Proportion of Positive Samples: a Cohort Study of 64 *Cutibacterium acnes* Bone and Joint Infections

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ABSTRACT If a bone or joint infection is suspected, perioperative antibiotic prophylaxis is frequently withheld until intraoperative microbiological sampling has been performed. This practice builds upon the hypothesis that perioperative antibiotics could render culture results negative and thus impede tailored antibiotic treatment of infections. We aimed to assess the influence of antibiotic prophylaxis within 30 to 60 min before surgery on time to positivity of microbiological samples and on proportion of positive samples in *Cutibacterium acnes* bone and joint infections. Patients with at least one sample positive for *C. acnes* between January 2005 and December 2015 were included and classified as having an "infection" if at least 2 samples were positive; otherwise they were considered to have a sample "contamination." Kaplan-Meier curves were used to illustrate time to culture positivity. We found 64 cases with a *C. acnes* infection and 46 classified as having a *C. acnes* contamination. Application of perioperative prophylaxis significantly differed between the infection and contamination groups (72.8% versus 55.8%; $P < 0.001$). Within the infection group, we found no difference in time to positivity between those who had or had not received a perioperative prophylaxis (7.07 days; 95% confidence interval [CI], 6.4 to 7.7, versus 7.11 days; 95% CI, 6.8 to 7.5; $P = 0.3$). Also, there was no association between the proportion of sample positivity and the application of perioperative prophylaxis (71.6% versus 65.9%; $P = 0.39$). Since perioperative prophylaxis did not negatively influence the microbiological yield in *C. acnes* infections, antibiotic prophylaxis can be routinely given to avoid surgical site infections.

KEYWORDS *Cutibacterium acnes*, *Propionibacterium acnes*, perioperative antibiotic prophylaxis, osteomyelitis, joint infection, biofilm, intraoperative diagnostic

In orthopedic surgery, antimicrobial prophylaxis is routinely given to reduce the risks for surgical site infection and colonization of implanted orthopedic devices (1, 2). It is recommended to give an antibiotic agent with bactericidal effect within a window of 30 to 60 min prior to skin incision in order to target skin commensal bacteria, such as staphylococci, streptococci, or cutibacteria (2). Despite correctly applied antibiotic prophylaxis, orthopedic bone and joint infections still occur in about 1 to 10% of cases (3). These orthopedic bone and joint infections are typically caused by microorganisms growing in biofilms. Usually, these biofilms are heterogeneously distributed, which is challenging for an accurate localization of infection for diagnostic sampling (4). Biofilm microorganisms are in a metabolically inactive, nonreplicating state that makes them tolerant to our immune system and to antibiotics (5). Furthermore, biofilm bacteria are enclosed in a polymeric matrix, which protects them from antimicrobial agents and immune responses; biofilm bacteria are therefore difficult to reach, extract, and culti-

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vate (4, 6). All of these factors contribute to the challenge of diagnosing biofilm infections, including bone and joint infections. Due to these difficulties, when a bone or joint infection is suspected and surgical treatment is necessary, application of perioperative antibiotic prophylaxis is often withheld, with the goal of increasing the microbiological yield of positive intraoperative biopsy cultures to identify the pathogen (7–10). Only knowing the causative microorganism of the infection allows a tailored long-term antimicrobial treatment.

However, recent studies (11–15) have shown that exposure to antibiotic agents as perioperative single-shot prophylaxis ahead of intraoperative microbiological sampling is not associated with an increase in culture-negative results. Furthermore, studies claim that perioperative antibiotic prophylaxis is needed in septic orthopedic surgeries, since it significantly reduces infection rates (16–18). However, these studies were of small sample size, and the heterogeneity of the infections, including both virulent and low-virulent pathogens, is a major concern.

Cutibacterium acnes is a slow growing pathogen that is often involved in bone and joint infections (19) and is therefore qualified for studying the effect of perioperative antibiotic prophylaxis in orthopedic settings. Since previous studies primarily assessed the influence of perioperative prophylaxis on intraoperative culture results, studies examining the number and proportion of positive samples and the time to positivity or confirmation of the infection are lacking.

This study builds upon prior results from a large and homogenous cohort of patients with suspected *C. acnes* bone and joint infections (6). We aimed to assess the effect of perioperative antibiotic prophylaxis on time to positivity of *C. acnes* samples, which is a crucial factor for the physician with regard to further therapeutic management. Furthermore, we evaluated the number of positive samples and the time to confirmation of *C. acnes* infections in patients with and without perioperative antibiotic prophylaxis.

MATERIALS AND METHODS

Study population. We retrospectively included patients from the University Hospital Balgrist in Zurich, Switzerland, with at least one positive intraoperative sample for *C. acnes*, isolated between January 2005 and December 2015. We excluded patients with no available data on antibiotic prophylaxis at the time of surgery. Since antibiotic treatment might influence the time to positivity of *C. acnes* growth, we also excluded samples from patients who had taken antibiotics for $\geq$24 h within 14 days prior to sample acquisition. The University Hospital Balgrist in Zurich is an orthopedic clinic specializing in bone and joint infections. Approximately 5,000 surgical procedures are performed annually.

For clinical and demographic parameters at the time of diagnostic workup, the patient clinical database of the orthopedic clinic and the prospective database of the infectious diseases consultation service were accessed. Microbiological data were collected using the database of the Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland.

Within the same patient, same hospitalization period, same surgery, and same infection site, all samples were clustered as one diagnostic set per patient case, regardless of whether the sample came back positive or negative. Patients were grouped into the following two groups: the "infection" group if *C. acnes* was detected in at least two different samples within the same patient case, and the "contamination" group if there was only one sample positive for *C. acnes*. In order to ensure an accurate allocation to one of the two groups, only cases with three or more analyzable samples were included in this analysis (10, 20).

The study was approved by the institutional review board in Zurich, Switzerland (KEK Zurich number 2016-00145).

Analysis and statistical methods. For each sample of a patient diagnostic set, we collected details about the diagnostic method used for detection of *C. acnes*, such as tissue or bone samples, sonication fluid, synovial fluid or wound swab, and Gram staining.

We calculated time to positivity of *C. acnes* growth for each positive sample as the difference in days between start of microbiological culture and identification of *C. acnes*. Within the infection group, time to positivity referred to culture positivity of the second positive sample to confirm the infection and account for possible contamination.

We analyzed the proportion of positive microbiological samples (ratio of positive samples to the total of all samples taken for each patient) in order to account for the larger number of samples taken if an infection was suspected during surgery. We performed a sensitivity analysis to assess potential associations and systematic distortion of the results by the larger number of samples per patient required to be classified into the infection group. We therefore conducted a Cox proportional hazards regression with robust standard errors, adjusted for the number of samples taken and allowing for clustering of samples within patients.

Statistical analysis was performed using Stata 15.0 SE (StataCorp, College Station, TX). We used parametric (Student's *t* test) and nonparametric tests (Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables) to compare variables on a patient or a sample level, whichever seemed appropriate.

We used Kaplan-Meier curves to illustrate the number of days from intraoperative sampling to culture positivity in both the infection and contamination groups. Differences between the times to positivity of both groups were analyzed by using log-rank tests.

Microbiological processing. (i) Diagnostic cultures. All the applied preanalytical and cultivation processes, including the incubation times of 10 days, have been previously described in detail (6). Tissue samples were vortexed, homogenized, and incubated on agar plates and thioglycolate broth; however, bone samples were inoculated in thioglycolate broth only. Explanted hardware was sonicated, and cultivated on agar based media and thioglycolate, as recently published (6). For the sonication samples, a threshold of 50 CFU/ml bacteria on agar plates was considered positive.

(ii) Time to positivity of *C. acnes* growth. As previously described (6), time to positivity was defined as the time (in days) between the start of microbiological culture and one of the following: (i) *C. acnes* forming typical colonies on agar plates, (ii) turbidity in thioglycolate broth, or (iii) a positive signal in blood culture bottles for which *C. acnes* was subsequently identified on agar plates.

RESULTS

Clinical data and perioperative antibiotic prophylaxis. (i) Patient level. A total of 110 patients, predominantly male (69.1%) and with a median age of 58.5 years (interquartile range [IQR], 50 to 68), contributed to overall 550 intraoperative samples collected between January 2005 and December 2015. Among the most common sample sites were shoulder ($n = 72$) and hip ($n = 25$), followed by knee ($n = 6$). In 87.3% patients, a prosthesis (58/110) or another foreign body (38/110) was present. In 64 patients (58.2%), an infection with *C. acnes* was diagnosed, defined by at least two positive samples, while *C. acnes* identification in only one sample in each of the remaining 46 patients (41.8%) did not fulfill the criteria of a proven infection and was therefore considered sample contamination.

We analyzed 550 samples; of these, 484 (88%) were tissue biopsy specimens (including wound swabs and fluids), 54 (9.8%) were sonication fluid from removed implants, and 12 were (2.2%) bone biopsy specimens. This distribution did not significantly differ between the infection group and the contamination group ($P = 0.49$). The mean number of samples taken per patient was 5.3 in the infection group (IQR, 4 to 8) and 4.5 in the contamination group (IQR, 3 to 6). In the infection group, a median of 3 samples (IQR, 2 to 5) was positive with *C. acnes*. Patient characteristics and sample specifications are shown in Table 1.

Out of the 64 patients in the infection group, 44 (68.8%) had not received perioperative prophylaxis until intraoperative biopsy specimens for microbiology had been taken, compared to only 23 (50%) in the contamination group ($P = 0.047$). If antibiotic prophylaxis had been applied, it was mostly cefuroxime (83.7%), followed by cefazolin (9.3%) (Table 1). Distributions of infection and antibiotic prophylaxis status among patients and samples are illustrated in Fig. 1.

(ii) Time to sample positivity. *C. acnes* was detected in a total of 274 out of 550 (49.8%) analyzed samples. Among those, the mean time to culture positivity as defined for each group was significantly shorter in the 228 samples of the infection group (6.04 days; 95% confidence interval [CI], 5.71 to 6.37) compared to that in the 46 samples of the contamination group (8.37 days; 95% CI, 7.69 to 9.05) ($P < 0.001$) (Fig. 2).

In order to investigate the influence of perioperative prophylaxis on cultivation time of *C. acnes* within a comparable group of patients, we assessed the time to sample positivity in the infection group only. Of all 342 samples of the 64 patients in the infection group, 72.8% (249/342) were collected from patients who had not been exposed to perioperative prophylaxis, compared to the low percentage of samples 27.2% (93/342) from patients with prophylaxis exposure (Fig. 1). However, the time to positivity within the infection group did not significantly differ between those samples collected from patients exposed to perioperative prophylaxis (mean 7.07; 95% CI, 6.4 to 7.7) and those not exposed to perioperative prophylaxis (mean 7.11; 95% CI, 6.8 to 7.5) ($P = 0.3$) (Fig. 2B). The sensitivity analysis confirmed that this finding was not affected

TABLE 1 Clinical characteristics of 64 patients with bone and joint infections caused by *C. acnes* (≥2 *C. acnes*-positive samples) and 46 cases with no infection (1 *C. acnes*-positive sample)

Clinical characteristic	No. of patients			*P* value
	Overall (%) (*n* = 110)	With infection (%) (*n* = 64)	With no infection (%) (*n* = 46)	
Patient characteristics				
Male gender (n [%])	76 (69.1)	45 (70.3)	31 (67.4)	0.84
Age (median [IQR]) (yrs)[a]	58.5 (50–68)	58.5 (47.5–68)	58.5 (51–69)	0.48
Sample sites (n [%])				0.06
Shoulder	72 (65.5)	47 (73.4)	25 (54.4)	
Hip	25 (22.7)	12 (18.8)	13 (28.3)	
Spine	5 (4.6)	4 (6.2)	1 (2.2)	
Knee	6 (5.5)	1 (1.6)	5 (10.9)	
Other	2 (1.7)	0 (0.0)	2 (4.2)	
Sample type (n [%])				0.38
Tissue and/or bone	79 (71.8)	48 (75.0%)	31 (67.4%)	
Sonication fluid	32 (28.2)	16 (25.0%)	15 (32.6%)	
Mean no. of samples (IQR)	5 (3–6)	5.3 (4–8)	4.5 (3–6)	<0.001
Median no. of positive samples per case (IQR)	2 (1–4)	3 (2–5)	1	
Presence of foreign body (n [%])				0.28
Prosthesis	58 (52.7)	31 (48.4)	27 (58.7)	
Other foreign body	38 (34.5)	27 (42.2)	11 (23.9)	
Perioperative prophylaxis, yes	43 (39.1)	20 (31.2%)	23 (50.0%)	0.05
Prophylaxis agent (n [%])				0.14
Cefuroxime	36 (32.7)	17 (26.6)	19 (41.3)	
Cefazolin	4 (3.6)	2 (3.1)	2 (4.4)	
Clindamycin	2 (1.8)	0 (0.0)	2 (4.4)	
Vancomycin	1 (0.9)	1 (1.6)	0 (0.0)	

[a]IQR, interquartile range.

by the total number of samples taken per patient (adjusted hazard ratio, 0.84 [0.60 to 1.18], $P = 0.31$).

(iii) Proportion of sample positivity. Perioperative antibiotic prophylaxis could also have an influence on the number of positive samples within a case. Overall, the

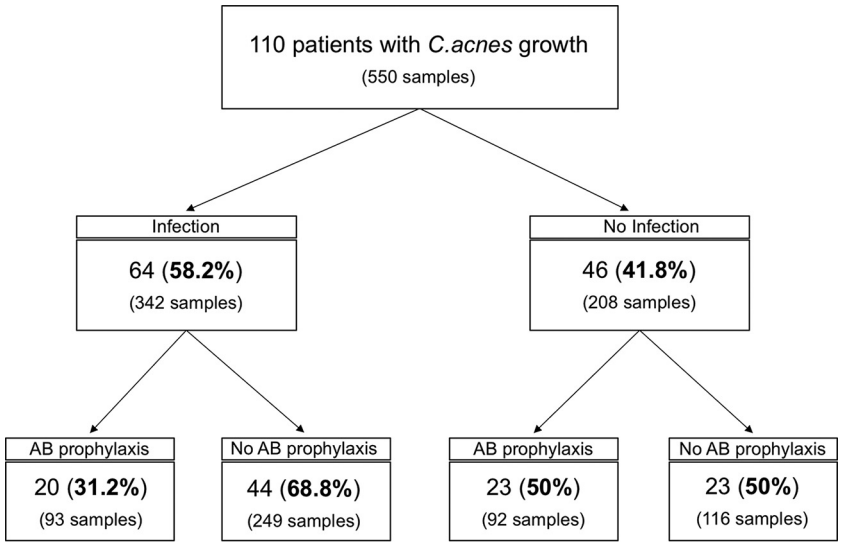

FIG 1 Distribution of infection and preoperative prophylaxis status among patients and samples. A total of 68.8% of the patients in the infection group did not receive antibiotic prophylaxis, compared to 50% of patients in the contamination group. AB, antibiotic.

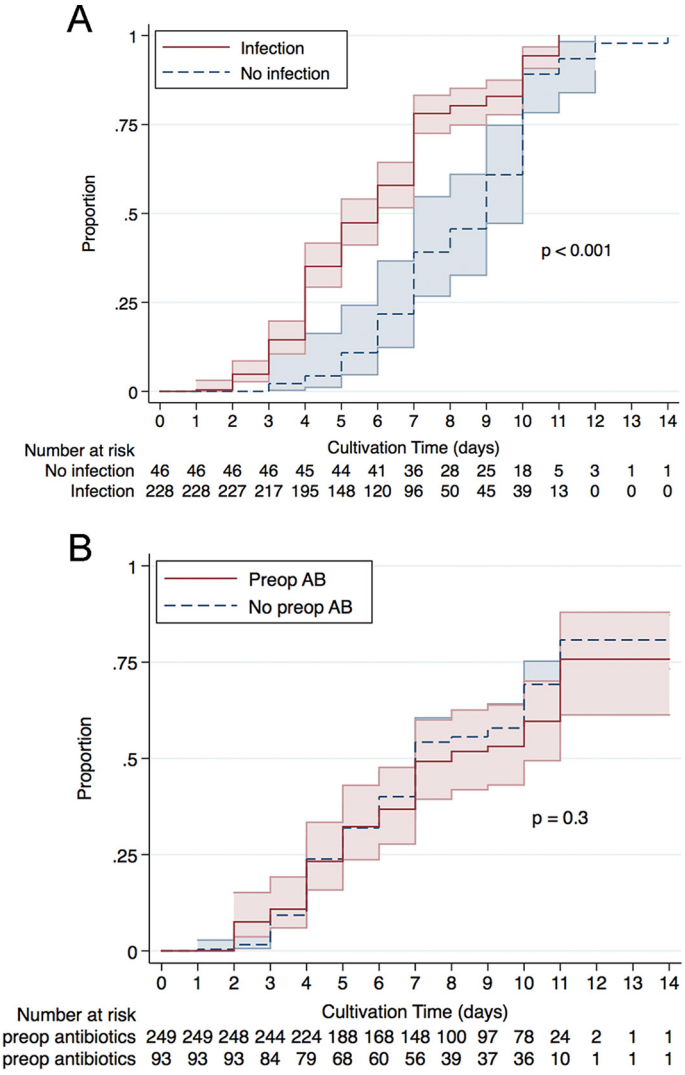

FIG 2 (A) Kaplan-Meier curve illustrating the proportion of sample positivity with *C. acnes* in all 274 positive samples, stratified by infection status (228 in the infection group versus 46 in the contamination group). The median time to positivity was 6 days for the infection group and 9 days for the contamination group (log rank $P < 0.001$). The colored areas represent the 95% confidence interval. (B) Kaplan-Meier curve illustrating the proportion of sample positivity with *C. acnes* in the 342 samples of the infection group, stratified by preoperative prophylaxis (93 in the prophylaxis group versus 249 in the no prophylaxis group). The median time to positivity was 8 days for the prophylaxis group and 7 days for the no prophylaxis group (log rank $P = 0.3$). The colored areas represent the 95% confidence interval. AB, antibiotic; periop, perioperative.

proportion of sample positivity among all 110 patients (infection and contamination groups combined) was 50.9% (95% CI, 45.4 to 56.5). In the 67/110 patients (60.9%) in which no perioperative prophylaxis had been applied, the proportion of sample positivity was 54.5% (95% CI, 46.8 to 62.1), while the remaining 43 patients (39.1%) with perioperative prophylaxis had a proportion of sample positivity of 45.5%. There was no significant difference in the proportion of sample positivity between the patients with and without perioperative prophylaxis ($P = 0.12$).

Among the 64 patients with a proven *C. acnes* infection, the proportion of sample positivity was 69.8% (95% CI, 63.8 to 75.8). Of these 64 patients, 44 (68.8%) had not received perioperative prophylaxis; their proportion of sample positivity was 71.6% (95% CI, 64.1 to 79.1). The remaining 20 patients (31.2%) with perioperative prophylaxis had a proportion of sample positivity of 65.9% (95% CI, 55.3 to 76.5). Hence, within the infection group, there was no significant difference in the proportion of sample

positivity between infection patients with perioperative prophylaxis and those without application of antibiotics before or during surgery ($P = 0.39$).

DISCUSSION

This is the first study analyzing the influence of perioperative prophylaxis on time to diagnosis and proportion of positive samples in a homogenous group of bone and joint infections caused by the same pathogen, *C. acnes*. As bone and joint infections cause significant morbidity for the individual and account for large health care expenses (21), the combination of surgical interventions and targeted biofilm-active antibiotic treatment against the causative pathogen is crucial in order to regain functionality (8). Therefore, timely microbiological identification is one of the mainstays in treating orthopedic infections. We showed that administering perioperative antibiotic prophylaxis did not affect the time to diagnosis of *C. acnes* infection, and therefore will not delay the timely identification of the pathogen in bone and joint infections. Our findings support the routine administration of perioperative prophylaxis, which has previously been shown to significantly lower surgical site infection rates (1, 2, 22). One systematic review (18) found a relative risk reduction of 81% of developing postsurgical wound infections among patients with total hip and knee replacements, if perioperative prophylaxis was administered correctly. Since hip and knee were also the most common surgical sites in our population, a risk reduction of this extent in wound infections would have major implications for the morbidity of our patients and thus our findings.

Proportion of positive samples within a diagnostic set in our study population of *C. acnes* infections did not differ between patients with and without perioperative prophylaxis (65.9% versus 68.8%). Bone and joint infections are typically biofilm-associated infections, in which bacteria are protected from antibiotic agents (8). In order to kill biofilm bacteria in the stationary phase, bactericidal antimicrobial substances (23) with a good ability to penetrate the biofilm, such as rifampin, are required (8). Cephalosporins, commonly used for perioperative prophylaxis, do not have these characteristics. Since the application of a preoperative single-shot antibiotic prophylaxis is primarily active against planktonic bacteria in the bloodstream and tissue, but is unable to penetrate the biofilm, antibiotic prophylaxis has no effect on culture positivity of intraoperative microbiological samples (13, 15, 24).

We recommend the routine administration of antibiotic prophylaxis, even when a *C. acnes* infection is suspected, as the administration of a single-shot antibiotic prophylaxis did not affect the intraoperative diagnostic yield. Our recommendation is in line with the American Academy of Orthopedic Surgeons (AAOS) guidelines from 2011 (15) as well as with a recently published systematic review (24) assessing the influence of perioperative prophylaxis on culture yield among patients with prosthetic joint infections. The authors of both studies (15, 24) did not find a significant difference between the prophylaxis and the nonprophylaxis groups, which would outweigh the risk of a postoperative infectious complication if perioperative prophylaxis was withheld. The recommendations of our study, the AAOS guidelines (15), and the systematic review (24) to routinely apply perioperative prophylaxis are not yet included in the French guidelines for bone and joint infections (9) nor in the Infectious Diseases Society of America (IDSA) guidelines (10) from 2013, which recommend to withhold antimicrobial prophylaxis when the preoperative risk of a prosthetic joint infection is high based on the results of the history, exams, sedimentation rate, C-reactive protein (CRP) level, and preoperative aspiration.

The strength of our study is the large, homogenous cohort of 64 cases with proven *C. acnes* bone or joint infection. This is, to our knowledge, the largest cohort study to date that focuses exclusively on this low-virulence and yet very relevant pathogen within the orthopedic context. For our study, we explicitly did not choose a virulent pathogen, such as *Staphylococcus aureus*, since identification of virulent pathogens is often less challenging, even if a short course of antibiotic treatment has been given prior to surgery. A further strength of our study is the novel aspect of our analysis,

including the comparison of time to positivity between different patient groups, as well as the analysis of the proportion of positive samples within the patient clusters. The long-running microbiological protocols for all bone and joint samples in our cohort secured the comparability of the culture results. A limitation of our study is the retrospective study design, which set certain restrictions in terms of availability of information and comparison to control groups.

In conclusion, based on to our results in patients with *C. acnes* bone and joint infections, perioperative antibiotic prophylaxis did not influence the intraoperative diagnostic yield of microbiological cultures. We therefore recommend that perioperative antibiotic prophylaxis in elective orthopedic infection operations should be routinely given and not be withheld until all intraoperative biopsy specimens are taken. On the one hand, this will minimize the risk of bacterial infection of the surgical field, and on the other hand, this will protect the newly implanted hardware.

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