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Administration of antibiotic agents before intraoperative sampling in orthopedic infections alters culture results

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KEYWORDS
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Summary *Summary:* Many physicians and surgeons think that prescribing antibiotics before intraoperative sampling does not alter the microbiological results.
Methods: Case-control study of adult patients hospitalized with orthopedic infections.
Results: Among 2740 episodes of orthopedic infections, 1167 (43%) had received antibiotic therapy before surgical sampling. Among these, 220 (19%) grew no pathogens while the proportion of culture-negative results in the 2573 who had no preoperative antibiotic therapy was only 6%. By multivariate analyses, pre-operative antibiotic exposure was associated with significantly more culture-negative results (odds ratio 2.8, 95% confidence interval 2.1–3.7), more non-fermenting rods and skin commensals (odds ratio 2.8 and 3.0, respectively). Even a single pre-operative dose of antibiotic was significantly associated with subsequent culture-negative results (19/93 vs. 297/2350; χ^2-test, $p = 0.01$) and skin commensals (17/74 vs. 274/2350; $p = 0.01$) compared to episodes without preceding prophylaxis.
Conclusions: Prior antibiotic use, including single-dose prophylactic administrations, is three-fold associated with culture-negative results, non-fermenting rods and resistant skin commensals.

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Introduction

When a patient with a suspected infection undergoes operative treatment, clinicians often withhold empiric antibiotic agents before intraoperative sampling for microbiological cultures. Similarly, if the patient has already been started on antibiotic therapy the clinician will often implement an antibiotic-free "window" before elective surgery. This decision is based on the belief that when the patient is receiving antibiotic treatment it inhibits bacterial growth, thereby reducing the ability to define the causative pathogen(s). There are, however, few data supporting, and none quantifying this risk. In fact, recent reports[1,2] suggest that prescribing antibiotic treatment before operative sampling does not increase the risk of culture-negative results. The few studies published on this issue principally investigated the number of culture-negative cases, and did not assess the potential for antibiotic pre-treatment selecting for gram-negative non-fermenting rods, antibiotic-resistant skin commensals[2] or monomicrobial infections.[1–3] Our university-affiliated medical center has a large septic orthopedic ward. We therefore conducted a retrospective, single-center study to try to quantify the effect of antibiotic administration before obtaining surgical samples in patients undergoing operative procedures for orthopedic infections. Specifically, our goal was to compare the rates of culture-negative specimens and the identity of pathogens isolated in patients who did or did not receive antibiotic therapy (including single-dose perioperative prophylaxis) before surgery.

Methods

Definitions

In the Orthopedic Service of Geneva University Hospitals, with approval of our local Ethics Committee, we have kept several data bases recording details of patients treated for osteoarticular[4–10] and soft tissue infections.[11–13] We included all adult patients hospitalized for orthopedic infections requiring surgery from January 2004 to January 2015. We defined infection clinically as the presence of intraoperative pus, together with other signs or symptoms such as new onset of pain, fever, warmth, redness, discharge or radiographic signs of implant loosening or the presence of sequestrae. We recorded whether the patient had diabetes mellitus or any immune suppression, such as active malignancy, immune-suppressive drugs (including glucocorticoids at a dose equivalent to 15 mg/d of prednisone), inadequately treated human immunodeficiency virus infection, cirrhosis Child C, pregnancy, splenectomy, agranulocytosis, or renal dialysis. We classified the following organisms as skin commensals: coagulase-negative staphylococci, corynebacteria, *Bacillus* spp, micrococci and propionibacteria.

To avoid data clustering, we included only the first episode of the same infection and eliminated recurrent episodes from further analysis. In contrast, we included new episodes for the same patient if the infection was at a different time or location. Other exclusion criteria were incomplete information regarding prior antibiotic use, and infections that did not undergo drainage (e.g., cellulitis), or infections caused by mycobacteria, brucella, parasites or fungi. We defined prior antibiotic exposure as receipt of systemic (not topical) administration of any agent during the 14 days prior to the surgical or drainage procedure. The 14 day period was chosen because it is the recommended "antibiotic window" period for arthroplasty infections[14] and represents a period beyond multiple half-lives of all administered antimicrobial drugs (the week-long acting dalbavancin and oritavancin were not available in Switzerland).

Microbiological analyses

The specimens for culture were transported from the operating theater or emergency department to the laboratory in the same building within 0.5–2 hours. Specimens collected during night shifts and on weekends were stored in the refrigerator up to 18 hours before being processed. The procedures corresponded mainly to CLSI (Clinical and Laboratory Standard's Institute) recommendations[15] and remained unchanged throughout the entire study period except for switching to EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing) in spring 2014.[16] The standard incubation period for cultures was 5 days. We do not sonicate in our hospital.[17] We accepted organisms growing in enrichment broths as pathogens, but did not use organisms identified only by polymerase-chain-reaction (PCR) assays,[3] serology,[18] Gram-or acridine orange-stained smears. These decisions were based on the fact that sonication requires explanted hardware, PCR was rarely used, and Gram-staining yields low performances in case of native septic arthritis[7] and hand phlegmona.[13] Thus, incorporating these auxiliary techniques into our final analysis could lead to inconsistencies.

Statistical analyses

Our primary outcome was the incidence of culture-negative results on operative specimens stratified by prior receipt of antibiotic therapy. We also were specifically interested in looking at the possible role of duration of pre-operative antibiotic treatment, duration of any antibiotic-free time windows, antibiotic treatment for perioperative prophylaxis, differences between antibiotics administered by the intravenous vs. oral route, and class of molecules. A secondary outcome was to determine if there was an effect on microbiological results by prior antibiotic treatment, with the following surrogate variables: monomicrobial vs. polymicrobial infections, presence of skin commensals or non-fermenting gram-negative rods. We performed group comparisons using the Pearson-χ^2 or the Wilcoxon-ranksum-test, as appropriate. We used an unmatched logistic regression analysis to determine associations with the outcome "culture-negative results". Since the pre-sampling antibiotic-free interval was censored at 14 days prior to surgery, giving a relatively short time window, we elected not to perform a formal Cox regression analysis. We introduced independent variables with a p value ≤ 0.20 in univariate analysis in stepwise fashion in the multivariate analysis; while we included antibiotic-related variables in every

case. We included 8 to 10 outcome events per predictor variable. We checked key variables for confounding, colinearity and interaction, the latter by Mantel—Haenszel estimates and interaction terms. Age, C-reactive protein serum levels (CRP), the duration of prior antibiotic use, and the antibiotic-free window before antibiotic sampling were analyzed both as continuous and categorical variables with cut-off levels at 50 and at 80 years, CRP values of 50 and of 200 mg/L, and antibiotic durations or windows with cut-offs at 1, 3—7, and 7—14 days. These stratifications were chosen according to clinically pertinent parameters, and the half-life duration of most β-lactam antibiotics, the most frequently used antimicrobial agents. The final model targeted the outcome "culture negative results" and included the following independent variables: age, CRP levels, bacteremia, immune suppression, infection type, exposure to prior antibiotics, duration of prior antibiotic use and of the antibiotic-free window. We considered p values ≤ 0.05 (two-tailed) as significant and used STATA™ software (9.0; College Station, USA).

Results

Infections and pathogens

Our databases provided information on 2740 episodes of orthopedic infections in 2612 patients. The patient's median age was 57 years, 871 episodes occurred in women and 1021 episodes were in immune-suppressed patients. Among the infectious episodes, 1202 (44%) were osteoarticular, including 321 prosthetic joint infections (12%), and 472 (17%) were septic bursitis cases. In total, 665 (24%) of the episodes were implant-associated, 319 (12%) were bacteremic and 429 (16%) involved the foot (mostly representing diabetic foot infections). A pathogen was identified in 2424 (88%) of cases: methicillin-susceptible *Staphylococcus aureus* was the most frequent organism (n = 1052; 38%); polymicrobial infection occurred in 572 (21%) episodes, including 258 episodes with non-fermenting gram-negative rods and 291 cases with skin commensals.

Antibiotic exposure

Within the study window of 14 days prior to surgery, systemic antibiotic therapy was given in 1167 (1167/2740; 43%) episodes. The regimens of antibiotic therapy varied considerably, with 154 different regimens, of which 718 (26%) episodes included at least some parenteral treatment. Among the specific agents, 706 (26%) episodes were treated with a β-lactam, 131 with a quinolone, and 222 received antibiotics that were administered once a day (e.g., ceftriaxone, vancomycin, daptomycin, teicoplanin or ertapenem). The median duration of antibiotic therapy prior to the surgical procedure was 4 days, and the formal median antibiotic-free window prior to drainage was 0 days.

Group comparisons

The patients whose episodes involved prior antibiotic exposure differed considerably from those without prior antibiotics (Table 1). Operative cultures from 2424 (88%) grew a pathogen. Of these organisms, 358 (15%) were resistant to the antibiotic(s) that had been administered within the 14 days before surgery, although the clinical response to treatment was favorable in the majority of cases.

Table 1 Comparison of patients with orthopedic infections who did or did not have a history of prior antibiotic use.

n = 2740	No prior antibiotics	Prior antibiotics	p value[a]
	n = 1573	n = 1167	
Median age	54 years	60 years	0.001
Median C-reactive protein level	67 mg/L	87 mg/L	0.001
Immune suppression[b]	502 (32%)	519 (45%)	0.001
Diabetes mellitus	307 (20%)	352 (30%)	0.001
Type of infection			
Osteoarticular infections	746 (47%)	456 (39%)	0.001
- Prosthetic joint infection	232 (15%)	89 (8%)	0.001
- Implant-associated infections	428 (27%)	237 (20%)	0.001
Bursitis	318 (20%)	154 (13%)	0.001
Foot infection	206 (13%)	223 (19%)	0.001
Bacteremia	173 (11%)	142 (13%)	n.s.
Causative pathogen(s)			
Staphylococcus aureus	709 (48%)	343 (36%)	0.001
Skin commensals[c]	170 (12%)	121 (13%)	n.s.
Non-fermenting gram-negative rods	99 (7%)	159 (17%)	0.001
Polymicrobial	304 (21%)	268 (28%)	0.001
Culture-negative	96 (6%)	220 (19%)	0.001

[a] Only significant p values ≤ 0.05 (two-tailed) are displayed.
[b] Immunosuppressive therapy, renal dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis.
[c] Coagulase-negative staphylococci, corynebacteria, propionibacteria, *Bacillus* species.

Overall, patients exposed to antibiotics prior to their operative procedure had a significantly higher proportion of negative intra-operative culture specimen results compared to those who did not have pre-operative antibiotics (19% versus 6%, $p = 0.001$). As shown in Table 1, prior antibiotic exposure as opposed to no exposure was associated with fewer infections caused by methicillin-susceptible *S. aureus* (36% versus 48%, $p = 0.001$), and more polymicrobial infections (28% versus 21%, $p = 0.001$) and infections with non-fermenting gram-negative rods (17% versus 7%, $p = 0.001$). Regarding the antibiotic-free window before intraoperative sampling, our analysis identified a cut-off of four days as a time-point, beyond which longer windows did not influence the incidence of culture-negative results (Fig. 1). In contrast, the duration of antibiotic prescription before sampling did not influence the culture-negativity (Fig. 2).

Stratified data

We investigated if culture-negativity and prior antibiotic exposure would be different within four large substrata of orthopedic infections: prosthetic joint infections, fracture-device infections, implant-free osteoarticular infections, and septic bursitis. The proportions of prior antibiotic exposure were 89/321 (28%), 148/346 (43%), 237/567 (22%), and 154/472 (33%), respectively. The corresponding culture-negative intraoperative results were 20/321 (6%), 23/346 (7%), 77/567 (14%), and 81/472 (17%), respectively. The culture-negativity was significantly less for arthroplasty infections than for septic bursitis (see Table 2).

Influence of prior perioperative antibiotic prophylaxis

A single pre-operative dose of antibiotic (given one hour before surgery) was recorded in 93 (3%) of the episodes, and it was significantly associated with subsequent culture-negative results (19/93 vs. 297/2350; χ^2-test, $p = 0.006$) and skin commensals (17/74 vs. 274/2350; χ^2-test, $p = 0.003$) compared to episodes without preceding prophylaxis. Of the 74 episodes that were culture-positive, 28 (38%) grew a pathogen that was resistant to the antibiotic given for prophylaxis, mainly non-fermenting gram-negative rods and skin commensals.

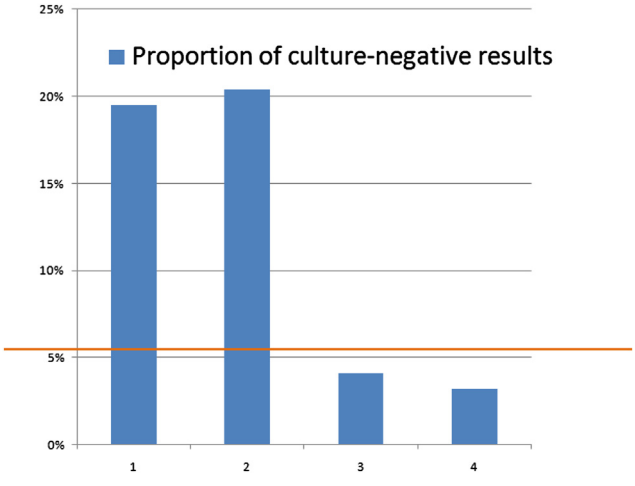

Figure 1 Proportions (in %) of culture-negative intraoperative samplings (vertical axis) compared to the duration of antibiotic-free window before sampling (in days; horizontal axis). The horizontal line is the proportion of culture-negative samples without prior antibiotic exposure.

Adjustment for case mix

As there were substantial differences in various demographic and clinical characteristics between the groups who did, versus those who did not, receive pre-operative antibiotic therapy, we performed a multivariate analysis to adjust for the case-mix. Prior antibiotic use, including single dose prophylaxis, was significantly associated with culture-negative results (odds ratio 2.8, 95% confidence interval 2.1—3.7). We were unable to detect a minimal duration of antibiotic-free window or a maximal duration of antibiotic exposure that was associated with negative intraoperative culture results. Likewise, there was no association of patient comorbidities, type of infections, administration route or specific antibiotic classes that was significantly associated to the risk for culture-negative results. Only the finding of bacteremia or a high serum CRP level was associated with an increased likelihood of a positive intraoperative culture. We could not incorporate many parameters into the final model because there were significant interactions and these are therefore only displayed as univariate results (Table 3).

Alteration of microbiological results following antibiotic exposure

In a further statistical analysis, we repeated the multivariate analysis to determine factors associated with specific microbiological results: polymicrobial infection, infections due to non-fermenting gram-negative rods (such as *Pseudomonas* spp or *Enterobacter* spp), or to skin commensals (coagulase-negative staphylococci, *Corynebacterium*, *Propionibacteria*, or *Bacillus* species). In all three separate analyses, the presence of bacteremia was negatively

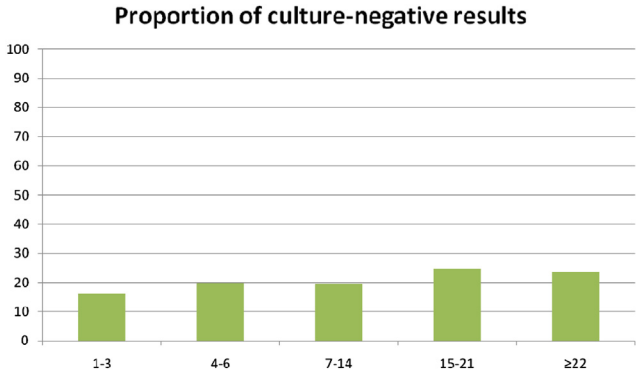

Figure 2 Proportions (in %) of culture-negative intraoperative samplings (vertical axis) compared to the duration of pre-operative antibiotic prescription (in days; horizontal axis).

associated with isolation of these groups of pathogens (odds ratio [OR] 0.3—0.4), whereas prior antibiotic use was associated with the isolation of non-fermenting rods (odds ratio 2.8) and skin commensals (odds ratio 3.0). Of note, all goodness-of-fit values were insignificant, and the ROC (receiver operating curve)-value was 0.80, highlighting an acceptable accuracy of all our final models.

Discussion

In this large cohort of 2740 episodes of osteoarticular and soft tissue orthopedic infections, 43% of all surgical patients had received antibiotic therapy before undergoing a surgical procedure during which material was sent for culture. Among the episodes in patients who had received antibiotic therapy, 19% grew no pathogens, while the proportion of culture-negative results in episodes without pre-operative antibiotic exposure was significantly lower, at 6%. Using multivariate analyses, prior antibiotic exposure was significantly and independently associated with negative operative culture results (OR 2.8) and isolation of more antibiotic-resistant pathogens (OR 2.8 for the detection of non-fermenting rods, and odds ratio of 3.0 for resistant skin commensals). The higher proportion of non-fermenting rods and skin commensals, because of prior antibiotic exposure, can be explained by altered (former) poylmicrobial infections, for which the susceptible part does not grow in contrast to naturally resistant organisms that are selected by commonly used antibiotics.

Our results are similar to most previous publications that have examined this issue. Among 3840 osteoarticular infections, Levy et al. reported that 9% were culture-negative cases, of which one-third were thought to be related to prior antibiotic exposure.[3] In a series of prosthetic joint infections reported from the Mayo Clinic, the overall incidence of culture-negative cases was 7%, half of which were patients who had received a prior course of antimicrobial therapy.[19] In all reports we found describing the use of PCR or sonication for explanted prosthetic joints, the authors report that prior antibiotic therapy reduced the sensitivity of periprosthetic tissue cultures.[3,17] In contrast, Ghanem et al. reported that among 172 patients with an infected total knee arthoplasty, there was no significant difference in culture-negative results among the 72 patients receiving preoperative prophylaxis compared with the 99 similar patients who did not (12 vs. 9%),[2] albeit their analysis was potentially underpowered.

Our results suggest that giving a single-dose of preoperative antibiotic prophylaxis has a similar effect on the culture results of operative specimens as more prolonged antibiotic treatment.[14,20—23] To the best of our knowledge, there are no data examining the effect of a delay of administering antibiotic prophylaxis of 10—20 minutes (the time needed to intraoperative access for infection). Burnett et al. investigated 26 infected (based on a prior positive puncture culture) total knee joints arthroplasties. After they administered a single dose of a targeted antibiotic agent, the intraoperative cultures grew all the previously known pathogens.[1] The authors concluded that a single perioperative antibiotic dose would not alter intraoperative culture results, although their study was small and biased to puncture-positive cases only. In our study, exposure to

Table 2 Group comparison of variables associated with results of culture (negative versus positive) of operative specimens.

n = 2740	Culture-negative	Culture-positive	*p* value[a]
	n = 316	n = 2424	
Median age	55 years	57 years	n.s.
Median C-reactive protein level	44 mg/L	80 mg/L	0.001
Bacteremia	15 (5%)	304 (13%)	0.001
Immune suppression[b]	109 (34%)	912 (38%)	n.s.
Diabetes mellitus	62 (20%)	597 (25%)	n.s.
Type of infection			
Osteoarticular	116 (37%)	1086 (45%)	0.006
- Prosthetic joint	20 (6%)	301 (12%)	0.001
- Implant-associated	43 (14%)	622 (26%)	0.001
Bursitis	81 (26%)	391 (16%)	0.001
Foot	44 (14%)	385 (16%)	n.s.
Parenteral antibiotic used	123 (39%)	595 (25%)	0.001
- Quinolone	26 (8%)	105 (4%)	0.001
- β-lactam	136 (43%)	570 (24%)	0.001
- Long acting agent[c]	33 (10%)	189 (8%)	n.s.
Median duration of antibiotic exposure	5 days	4 days	0.02
Median duration antibiotic "window"[d]	0 day	0 day	0.02
Prior antibiotic exposure	96 (30%)	220 (9%)	0.001

[a] Only significant *p* values $\leq$ 0.05 (two-tailed) are displayed.
[b] Immunosuppressive therapy, renal dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis.
[c] Vancomycin, teicoplanin, ceftriaxone, ertapenem
[d] Period between when antibiotic stopped and when specimen for culture taken.

Table 3 Odds ratios of independent variables associated with negative culture results on operative specimens (by univariate and multivariate logistic regression analyses).[a]

n = 2740	Univariate analysis	Multivariate analysis
Age (continuous variable, years)	1.0 (1.0–1.0)	n.a.
- 51–80 compared to <50	1.0 (0.8–1.2)	1.1 (0.8–1.5)
- >80 compared to <50	***0.5 (0.3–0.9)***	1.2 (0.8–1.8)
C-reactive protein (continuous variable, mg/L)	***1.0 (1.0–1.0)***	n.a.
- 51–200 compared to<50	***0.6 (0.4–0.8)***	***0.6 (0.4–0.8)***
- >200 compared to<50	***0.6 (0.4–0.8)***	***0.6 (0.4–0.8)***
Bacteremia	***0.4 (0.2–0.6)***	***0.4 (0.2–0.7)***
Immune suppression[b]	0.9 (0.7–1.1)	0.9 (0.7–1.2)
Diabetes mellitus	0.7 (0.6–1.0)	n.a.
Type of infection		
- Osteoarticular	***0.7 (0.6–0.9)***	n.a.
- Prosthetic joint	***0.4 (0.3–0.7)***	0.7 (0.4–1.1)
- Foot	0.9 (0.6–1.2)	0.8 (0.6–1.2)
Prior antibiotic exposure	***3.6 (2.8–4.6)***	***2.8 (2.1–3.7)***
- Single prophylaxis exposure	***2.0 (1.2–3.4)***	n.a.
- Quinolone	1.1 (0.7–1.7)	n.a.
- β-lactam	1.1 (0.8–1.4)	n.a.
Duration antibiotic use (continuous variable, days)	1.0 (1.0–1.0)	n.a.
- 3–7 compared to ≤2	1.3 (0.9–2.0)	1.1 (0.7–1.7)
- >7 compared to ≤2	***0.5 (0.4–0.7)***	1.5 (1.0–2.2)
Antibiotic window[c] (continuous variable, days)	0.9 (0.8–1.0)	n.a.
- 3–7 compared to ≤2	0.7 (0.3–1.5)	0.8 (0.3–1.7)
- >7 compared to ≤2	***0.3 (0.2–0.4)***	0.5 (0.2–1.2)
Parenteral administration	0.8 (0.6–1.0)	n.a.

[a] Results are displayed as odds ratio (95% confidence interval).**Variables in bold and *italic* are statistically significant (*p* value < 0.05).**

[b] Immune-suppressive therapy, dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis.

[c] Period between when antibiotic stopped and when specimen for culture taken.

a single dose of a parenteral preoperative antibiotic quadrupled the rate of a culture-negative intraoperative specimen. Additionally, it was associated with a significantly higher rate of antibiotic-resistant pathogens, specifically more non-fermenting gram-negative rods and skin commensals.

Our study has several important limitations: i) We only included adult patients hospitalized on an orthopedic ward at a single institution in a high-income country, factors that might limit generalizability of the findings. ii) We do not address the question if culture-negative operative specimens influence post-surgical empirical therapy or the outcomes of infections. Available literature suggests that the clinical remission rate for treatment of culture-negative prosthetic joint infections is the same as for culture-positive cases,[19] but a clinician's ignorance of the causative pathogens may lead to longer duration or broader-spectrum empiric antibiotic therapy compared to cases with known culture results.[24] In this study, we elected not to address the clinical consequences of altered microbiological results because the outcome of orthopedic infections depends on multiple parameters, e.g., removal of infected material, re-implantation procedures, number of debridements, isolated pathogens,[10,25–27] comorbidities, and type of infection (native joint arthritis,[5] infected arthroplasties,[8] infected fracture-devices,[4,6] chronic osteomyelitis,[9] bursitis[12] or soft tissue infections[11]). Performing a multivariate analysis with this large case-mix is not possible unless we stratify remission analyses into six strata, which would be inordinately complex and lead to comparisons of small groups. However, in all our prior publications targeting one specific type of orthopedic infection, empirical therapy or prior antibiotic use did not alter remission rate. We invite the interested reader to consult our prior publications.[5–9,11,12] Likewise, the choice of the duration and spectrum of antibiotic coverage at our medical center could be biased, as we are infectious diseases consultants specialized in orthopedic infections and experts in antimicrobial stewardship; hence potentially able to streamline the empiric choice basing only on local epidemiological data.[28] iii) We did not use results of sonication,[17] PCR[3] or serology[18] procedures; while these auxiliary techniques are designed to identify pathogens that fail to grown on culture because of prior antibiotic exposure but their usefulness is not entirely clear. For example, in one study done in France, among all culture-negative osteoarticular infections only 9% were PCR-positive.[3] Concerning sonication, it only applies for removed hardware, but not for the majority of infections such as soft-tissue infections, bursitis, implant-free osteomyelitis, native septic arthritis or implants that has been kept in place. Overall, the potentially sonicable part of all infections in septic

orthopedics and our database is at maximum 10%. We recommend the consultation of specific literature regarding culture-negative sonication results in presence of prior antibiotic prescription. iv) There is probably another potential difference concerning the impact of preoperative antibiotics in patients with acute infection, due to rapidly growing bacteria, with high inoculum in comparison with patients with chronic infection or productive sinus tracts, with slow-growing bacteria embedded in biofilm and associated with low inoculum. We could not analyze this particular aspect. v) We ignore the exact reasons of different surgeons and physician to prescribe antibiotics before intraoperative sampling. Theoretically, there might be several reasons such as false beliefs, conservative approaches that failed, patients' preferences and social status, composition of the emergency department teams, fear of a worse outcome, fear of legal consequences, prior antibiotic prescription for another reason than the later orthopedic infection, a mixed of all, or other reasons that we are not even thinking about. Unfortunately, our records rarely indicate why exactly the patients received preoperative antibiotics, and if one or several healthcare workers were involved in the decision. Nevertheless, the objective distinction of both patient populations as seen in Table 1 reveals some insight for our center. The fact that patients with osteoarticular or implant infections receive less likely prior antibiotics, does not support ignorance by the treating surgeons. In contrast, the higher proportion of immunesuppressed patients among the group with prior antibiotic exposure either suggests fear facing the patient's frailty, or administration of antibiotics for any other reason than the actual infection episode. v) Finally, we analyzed only the first intraoperative sampling. It is clear that adding the results of subsequent surgeries, the proportion of culture-negative results would be much higher.

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Transparency declarations and potential conflicts of interests

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IU and CL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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