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

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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; $\chi^2$-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-$\chi^2$ 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 $\leq 0.20$ in univariate analysis in stepwise fashion in the multivariate analysis; while we included antibiotic-related variables in every