

G80: What is the most optimal antibiotic treatment of patients with implant associated infections caused by *Cutibacterium acnes*?

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Answer: Although a number of antibiotics are available to treat orthopedic-implant infections caused by *Cutibacterium acnes*, the type, dose and route of administration of optimal antibiotic(s) remain unknown.

Level of Evidence: Limited

Delegate Vote:

Rationale:

The role of *Cutibacterium acnes* as the cause of orthopedic-implant associated infections has been recognized for many decades.^{1,2} Prospective cohort studies evaluating the microbiologic epidemiology of periprosthetic joint infections (PJIs) have found 6-10% of all cases to be a result of *C. acnes*.^{3,4} *C. acnes* has been reported to cause infections of almost all orthopedic implants, but has particular predilection for shoulder hardware, likely secondary to the high rates of colonization of the axilla.⁵ In fact 31-70% of shoulder PJIs are secondary to *C. acnes*.⁵ In addition *C. acnes* is a common cause of shoulder fracture-fixation hardware infections and infections following rotator cuff repair.⁶ *C. acnes* is also a commonly encountered cause of latent spinal hardware infection, approaching 20% of cases in some series.⁷⁻¹⁰ But despite its increasing recognition as an important pathogen in implant-related infections the literature pertaining to the optimal antibiotic treatment of *C. acnes* implant infections are very limited; treatment recommendations are primarily guided by *in-vitro* antibiotic susceptibility data and small retrospective (and largely heterogeneous) clinical studies.¹¹ To evaluate the most optimal antibiotic treatment for patients with implant-associated infections caused by *C. acnes* a comprehensive literature search was conducted. Searches were conducted in PubMed and Embase using combinations of keyword terms, including “antibiotic*,” “arthroplasty,” “spine implant*,” “orthopedic surgery,” “joint prosthesis,” “periprosthetic joint infection,” “PJI,” “*Propionibacterium acnes*,” and “*Cutibacterium acnes*.” The search initially identified 706 potentially relevant studies. Titles and abstracts were screened independently by two reviewers; 54 studies were selected for an in-depth review of which 33 were included.

C. acnes is sensitive to a broad range of antibiotics, including beta-lactams, (e.g. penicillin, cephalosporins, and carbapenems), glycopeptides, clindamycin, linezolid, fluoroquinolones, daptomycin and tetracyclines;^{6,9,12,13} it is intrinsically resistant to metronidazole. However, interpretation and comparison of published *C. acnes* susceptibility data is complicated by differences in or lack of species-specific breakpoints used. The current Infectious Diseases Society of America (IDSA) guidelines recommend IV penicillin or ceftriaxone as first line therapy for periprosthetic joint infections, and clindamycin (IV or PO) or vancomycin as second-

line.¹⁴ Guidelines of implant infections published by the Société de Pathologie Infectieuse de Langue Française (SPILF) suggest amoxicillin, cefazolin, ceftriaxone or clindamycin.¹⁵

There has been some concern about changes in the prevalence of resistance to various antibiotics; for example, a large meta-analysis of 39 studies investigating the prevalence of *C. acnes* antibiotic resistance reported the following rates: co-trimoxazole - 9%, doxycycline - 8%, levofloxacin - 6%, ciprofloxacin - 5%, minocycline - 2.5%, and alarmingly, clindamycin - 31%. Significant geographic variation was found, as well as temporal trends suggesting rising rates.¹⁶ It is important to note, however, that this meta-analysis, and much of the published data regarding *C. acnes* antibiotic susceptibility, is based on isolates from dermatologic specimens, often in patients undergoing (or failing) antimicrobial treatment for acnes vulgaris. Isolates from non-dermatologic specimens show much lower rates of resistance.¹⁷ A ten-year single-center study analyzing 2,497 *C. acnes* isolates, in which the orthopedics department submitted 51.9% of specimens, reported all strains to be sensitive to amoxicillin, ceftriaxone, vancomycin, daptomycin, linezolid, and moxifloxacin. 4.1% of strains were clindamycin-resistant -- but underscoring the importance of the site of specimen acquisition, the authors noted that over half of these clindamycin-resistant strains were from dermatologic samples (and dermatologic samples only made up 21.5% of the total isolates tested), suggesting these specimens may have been impacted by treatment for acnes vulgaris. 2.2% of the strains were resistant to doxycycline and 1.1% resistant to rifampin. These findings correlate with smaller studies reporting on clinical specimens taken from infected orthopedic implants.^{11,13,18,19} Even with the lower rates of resistance; however, these studies do emphasize the need to employ antimicrobial susceptibility testing on all clinical *C. acnes* orthopedic specimens to help guide treatment; most notably, resistance to clindamycin was still found in 2.0-9.0% of isolates in these studies.

The body of literature about the efficacy of specific antibiotic regimens for treating *C. acnes* orthopedic implant infections is limited. Conducting research assessing the treatment of PJIs and other orthopedic implant infections, regardless of their microbiologic cause, is challenging for many reasons. These uncommon infectious complications require extended follow-up to assess outcomes, making it difficult to amass sufficient patients to power studies appropriately. In addition, heterogeneous presentations, variations in approach to complex surgical and antibiotic treatments, and the array of co-morbidities make confounding variables challenging to control, prospectively or retrospectively. However, *C. acnes* implant infections are an increasing challenge to study secondary to both the difficulty distinguishing septic from aseptic failure and, because of its frequent isolation as a contaminant in orthopedic specimens, the difficulty determining the clinical significance of positive culture results.²⁰

The available clinical studies of *C. acnes* implant infection are all retrospective in design and are typically small single-center observational cohorts with historical controls. Only very few of these studies stratify clinical outcomes by the specific antimicrobial treatment, and there are too few to draw meaningful conclusions regarding which regimen is optimal.²¹⁻²³ As expected, most of these studies assessed patients with *C. acnes* PJIs, primarily those of the shoulder. Studies of non-PJI *C. acnes* implant infections are even more difficult to parse given the lack of accepted diagnostic criteria to differentiate between contaminant and infection. This issue was highlighted in a study by Tai, *et. al*¹⁰ who reported retrospectively on 55 patients treated for *C.*

acnes spinal implant infections. Relapse rates were low, with an annual failure rate of 7.0%. However, 25% of the patients never actually received any antibiotics. A subgroup analysis showed that the failure rate was only slightly higher in the untreated patients; the authors suggested this finding may indicate that their diagnostic criteria, relying mainly on the presence of 2 or more positive cultures for *C. acnes*, may not have been sufficiently specific.

The role of adjunctive treatment with rifampin for *C. acnes* implant infections remains unclear. *C. acnes* is commonly sensitive to rifampin but is not reliably effective as monotherapy.²⁴ However, rifampin has been demonstrated in both *in-vitro* studies and animal-models to have excellent efficacy against *C. acnes* biofilm.^{25,26} Based on these findings, the British Elbow and Shoulder Society advocated for the addition of rifampin in the setting of retained *C. acnes* hardware infections.²⁷ But clinical data supporting this approach is lacking. The largest study addressing rifampin-based combination therapy for *C. acnes* reported on the outcomes of 187 patients with *C. acnes* PJIs; 43.3% of the cohort was treated with rifampin-based combination therapy.²⁸ No statistically significant difference in outcomes was reported between the two groups, even after adjusting for surgical treatment (DAIR v exchange procedure). This finding aligned with the results of several other smaller studies, all also showing no benefit with the addition of rifampin.^{11,29,30} Of note, only a minority of the patients in these 4 studies underwent DAIR; most had removal of all infected hardware. Interestingly, a 2022 meta-analysis assessing the role of rifampin in the treatment of PJIs reported, based on the inclusion of 2 of these studies (Kusejo *et.al*²⁸ and Jacobs *et.al*²⁹), actually did find a protective effect when rifampin was added, albeit with wide confidence intervals (0.44, 95% CI 0.22-.089).³¹ An even more recent meta-analysis assessing the effectiveness of rifampin-based combination therapy in a wide array of orthopedic implant infection, which included all 4 of these studies, a subgroup analysis found that rifampin-based treatment led to higher cure rates, with a RR of 1.11 (95% CI 1.01-1.22, p = .03), although the authors acknowledged the certainty and quality of the evidence was low.³² A fifth retrospective study published too recently to be included in either of these meta-analyses found no benefit to rifampin-based combination therapy in 70 patients undergoing exchange arthroplasty for chronic *C. acnes* shoulder PJIs.³³

In conclusion, based on available data, the dose, type, and route of administration of optimal antibiotics for treatment of orthopedic-implant infections caused by *C. acnes* remains unknown.

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