QUESTION 11: What is the most effective antibiotic in the treatment of C. acnes periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. High rates of susceptibility to narrow spectrum beta-lactams make these a good initial intravenous (IV) option, though the optimum oral switch is not known. The role of rifampin is controversial. Prospective clinical studies are required to determine the optimal antimicrobial therapy for C. acnes PJI.

LEVEL OF EVIDENCE: No evidence

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is an anaerobic gram-positive bacillus and a common skin commensal found deep in sebaceous glands and hair follicles. As well as being commonly implicated in acne vulgaris, it is a well-recognized pathogen of device related infection including prosthetic joints [1–4].

The ability of C. acnes to form biofilm is a major virulence factor in the development of these infections, including PJI, and is an important consideration for optimizing treatment strategies. Management should follow well recognized guidelines of a combination of surgery and targeted antibiotic therapy [5–7], though this has been challenged by at least one retrospective analysis [8]. Pragmatically, however, without doing prospective studies and controlling for the surgery performed, the duration of therapy and individual host factors, comparisons of different antibiotic regimens in the real world are very difficult.

This problem is compounded by the difficult issue of determining the significance of cultured C. acnes from orthopaedic specimens, as it is a common and well-recognized contaminant. It has been shown to be present in fluid washed across the skin incision [9], has been found on surgeons’ gloves after handling the subdermal layer [10] and is not reliably removed from the skin by surgical skin antisepsis [11]. The multiple sampling method of Atkins et al. [12] is commonly used to aid interpretation of the significance of C. acnes isolates, with one specimen positive out of three to five usually being deemed a contaminant [12]. The recommended duration of incubation of enrichment broths has been extended in recent years to 10 to 14 days to improve the pick-up rate of relatively slow-growing C. acnes in these samples. By increasing the isolation of significant isolates, however, the rate of contaminants also increases and requires careful interpretation [13]. It has been suggested that those isolated from true infections flag earlier than those that represent contamination. Sonication is recommended by some to improve pick-up rates of C. acnes associated with biofilm [14]. Some authors have gone further, by creating scoring systems to aid identification of true C. acnes infections [3,4].

For these reasons, accurate identification of C. acnes PJIs retrospectively is fraught with difficulties and thus interpretation of the outcome data comparing treatment strategies is very limited. The clinical details are imperative to aid interpretation. As well as varying in the clinical information available, retrospective studies also often span many years or decades, and straddle changes to sampling methods, culture methods and recommended duration of enrichment cultures. These differences further limit the ability to draw detailed comparisons between different interventions.

In vitro susceptibilities of C. acnes are reported widely. Surveillance studies show it remains susceptible to many antibiotics commonly used in treatment of bone and joint infection, but with increased and variable resistance to macrolides, clindamycin, tetracyclines and trimethoprim-sulfamethoxazole. A European surveillance study showed wide variations in rates of resistance across Europe, confirming the need to undertake susceptibility testing for individual isolates [15] and this has been replicated in other smaller series [15,16]. Looking at isolates from clinical specimens taken at shoulder surgery, Crane et al. showed that rates of resistance to beta-lactams (e.g., penicillin, amoxicillin, cefalozin and ceftriaxone) remained very low [17,18]. However, they found slightly higher minimum inhibitory concentrations (MICs) to vancomycin and taking that information with the minimum biofilm eradication concentration (MBEC) from other studies [19,20], vancomycin may be less favorable than alternatives in the context of biofilm. This study also looked at quinolones (ciprofloxacin and moxifloxacin) but not levofloxacin and showed high rates of susceptibility.

It is well-recognized that the susceptibility of microorganisms is dramatically reduced in biofilms. For infections with staphylococci, there is good evidence for the use of rifampin in combination therapy for its biofilm effect. The use of dual therapy with rifampin for C. acnes infections is theoretically attractive, though there is controversy in the literature. Baybost et al. found that linezolid plus rifampin led to relapse-free eradication after 14 days compared to linezolid alone [5]. Interestingly, in this study, penicillin alone was as effective as linezolid and rifamcin, but the effect of rifampin and penicillin was not examined. Tafin et al. in 2012 used an experimental foreign-body infection model to determine MIC and MBEC with and without rifampin for C. acnes from cage fluid and from explanted cages [19]. There was good activity of all antimicrobials tested for the planktonic forms, but rifampin was needed for activity in the biofilm. They used an in vivo animal model to evaluate susceptibility to levofloxacin, vancomycin, daptomycin and rifampin. The highest cure rate was found with daptomycin and rifampin (63%) followed by 46% for vancomycin.
and rifampin combination. Emergence of rifampin resistance associated with the presence of the rpoB gene has, however, been shown to occur in vitro [21].

Combination therapy for C. acnes has been further examined in vitro by Khassebaf et al. [15] who took C. acnes isolated from orthopaedic implant infections and carried out susceptibility testing in addition to looking for synergistic, additive and antagonistic effects of combinations. None of the antimicrobials examined were synergistic with each other and antagonistic effects were rare. Interestingly, the combination of rifampin and benzyl penicillin showed an additive effect on almost 50% of isolates tested. However, a retrospective cohort study by Jacobs et al. [22] showed no significant difference in success after two years between groups treated with combination antimicrobial treatment including rifampin (88%) or not including rifampin (82%). The most used antimicrobial in combination with rifampin was clindamycin.

The performance of these antimicrobials in clinical studies is not easy to assess and there are very few published good quality studies with no prospective studies identified and limited utility of retrospective studies. Over a decade ago, Zeller et al. conducted a retrospective cohort study of 50 patients with C. acnes PJI [23]. Treatment involved surgery with antibiotics for the majority of patients. Intravenous therapy with cefazolin and rifampin was administered to 24/50 patients and clindamycin with rifampin to 11 cases for a duration of 5 +/- 2 weeks followed by oral step down for a further 16 +/- 8 weeks. Oral regimens were similar to the IV regimes: cephalexin and rifampin or clindamycin and rifampin [23,24].

Reimuller’s retrospective review of a tertiary infection center database included 24 cases of C. acnes PJI over 14 years [25]. A strength in this study, despite it being retrospective, was the use of contemporaneous clinical diagnosis of infection alongside the microbiological diagnosis. All patients underwent surgery and were treated with antibiotics but the specifics of antimicrobial treatment are not given, other than stating that they followed recommendations by Zimmerli [7] and were guided by the specific microbiological diagnosis. Surveillance studies suggest C. acnes remains highly susceptible to beta-lactams which are attractive from an antimicrobial stewardship point of view and are commonly used and recommended in Infectious Disease Society of America (IDSA) guidelines [4–7,22,26,27]. Increasing rates of resistance for clindamycin and doxycycline are seen and antimicrobial therapy must therefore be based on the susceptibility testing of infecting pathogens determined using accredited methods. Additive or synergistic testing might be helpful, but the utility of this needs corroboration in clinical studies. Determining an appropriate targeted regimen at this stage can only be based on in vitro susceptibilities, on knowledge of oral bioavailability and bone penetration and on an individual risk/benefit assessment for the use of rifampin and other agents. Both the best oral antimicrobial and the role of rifampin as part of combination therapy remain unclear and well conducted prospective RCT studies are needed to help answer these questions.

REFERENCES

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