SH63: What is the optimal oral antibiotics for chronic suppression?

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Response: There may be a role for suppressive antibiotic treatment (SAT) following the management of shoulder PJI. However, there is no specific data in the shoulder literature regarding the choice of antibiotic therapy or duration of therapy. Selection of antibiotic type should be dictated by infection characteristics in consultation with Infectious Disease specialists when available.

Strength of Recommendation: Limited

Delegate Vote: 53 (100%) agree; 0 disagree; 0 abstain

Rationale: Suppressive antibiotic treatment (SAT), also termed Chronic antibiotic suppression (CAS), refers to the administration of antibiotics in the long term or indefinitely following the diagnosis of PJI. It is considered a "noncurative" strategy with the aim of reducing symptoms and delaying or preventing the progression of PJI. SAT is used when there is evidence of persistent prosthetic joint infection (PJI) after attempted surgical and antibiotic eradication, or it may be a treatment option for patients who have no signs of ongoing infection but refuse further operations or are not optimal surgical candidates due to significant medical comorbidities and frailty or would require limb-threatening surgery or amputation should infection relapse or recur.

There was consensus at the 2018 Proceedings meeting that SAT may have a role in the management of selected cases of periprosthetic infection of the shoulder, however the systematic reviews at that time failed to identify a significant number of shoulder PJI cases.[1] There have been no SAT papers with significant numbers of shoulder infections since, and none describing the choice of antibiotics or appropriate duration when used in shoulder infections. In Cortes-Penfield's recent extensive retrospective review of SAT following DAIR, zero shoulder patients were described from 33 studies reviewed.[2] There also remains ambiguity in the hip and knee arthroplasty infection literature surrounding the benefits and potential drawbacks of SAT because of a lack of comprehensive high quality randomized controlled trials. Data published is mostly from retrospective cohort and single-center studies with a small sample size, heterogenous populations, with varied definitions of SAT, types of infection and outcomes, and surgical management. [3] However, any recommendations for SAT in shoulder infections will need to be inferred from this hip and knee literature, or guidelines from national associations.[4]

Outcomes: Success rates from literature in treating periprosthetic shoulder infection the past decade have ranged between 60% and 93%. The highest success rates are observed in patients with a 'standard' prosthesis, low virulence infections, in particular *S. epidermidis* infection, and infections involving hips. Those who experienced multiple changes to their SAT regimen were more likely to fail. Critically, these studies do not demonstrate whether SAT prevents or merely delays subsequent PJI and long-term comparisons between indefinite SAT and time-restricted SAT strategies are lacking.[5-17]

When to use SAT. Cortes-Penfield proposed that following DAIR, SAT should be offered to most patients with at least 1 of the following factors: limited options for arthroplasty revision; recurrent PJI/prior PJI treatment failure; infection with difficult-to-treat pathogens; severe immunocompromise; and underwent arthroscopy instead of open DAIR, or polyethylene liner was not exchanged. The authors would consider SAT in patients with at least 1 of the following: significant co-morbidities; age >75years; and Gram-negative infection that cannot be treated with a fluoroquinolone.

Disadvantages of SAT. Potential drawbacks from SAT are those associated with long term antibiotic use, namely adverse events (AEs), intolerability, poor compliance, perturbations of the gastrointestinal microbiome, *C. difficile* infection, and the development of antimicrobial resistance.[18, 19] However, Cortes-Penfield review article reported AE in a median of 8.3% of patients, leading to cessation of SAT in only 3.1%. Reinecke's retrospective study noted that rifampin use might be a reason for the higher incidence of AEs compared to non-rifampin antibiotic treatment.[20] Cobo's review concluded that *C. difficile* infection occurs infrequently.[21]

Definition and duration of SAT. Most papers define SAT as oral antibiotics of >6 months duration. Hansenn et al's international cross-sectional survey concluded that Europe and Oceania consider SAT as lifelong antibiotic treatment of 'incurable infections', whereas in the US, SAT can be considered as an extended treatment duration after DAIR, aiming for cure. They recommended definitions for these two distinct treatment strategies. *Fixed term SAT* as prolonged antimicrobial therapy for a fixed duration of 6–24 months with the main goal of curing the infection. Or *Indefinite SAT* as antimicrobial therapy with an undetermined duration with the main goal to prevent a relapse.

Antimicrobial regimens. The choice for the type of SAT is individualized and should ideally be determined by an Infectious Disease physician or Medical microbiologist. The choice is determined by antibiotic susceptibilities of the cultured micro-organism(s), patient factors including antibiotic allergies, medication history, co-morbidities and organ dysfunction, and the expected (long-term) side effects of the antibiotic. Patients should be monitored and followed up in the long term, ideally in a multi-disciplinary setting using Complex Outpatient Antibiotic Therapy (CoPAT) principles. CoPAT can reduce the risk of serious antibiotic related AE's and improve patient adherence, optimising clinical efficacy.

In the previously cited international survey, most respondents would lower the standard therapeutic dosage for SAT, as both frequency and dose reduction may improve tolerability and therapeutic compliance. Hansenn et al's observational study reported no difference in failure-free survival between patients treated with low-dosage compared to normal-dosage SAT. [23] More data are necessary to inform on the effectivity and risk of antimicrobial resistance development of low dosed SAT. In general, low doses should not be used initially, at least until a reduction in inoculum has been achieved. Since SAT is intended to reduce symptoms and local inflammation by reducing the bacterial load, antibiotics with less activity against bacteria in biofilm are useful e.g. beta-lactams. Monotherapy rather than combination therapy is preferable, and rifampicin is avoided by most physicians because of side effects and tolerability issues. Pradier et al's retrospective study of 78 patients receiving doxycycline suggested that this antibiotic was an effective and well tolerated when used for SAT. [22]

The Infectious Diseases Society of America's (IDSA) 2013 guideline on PJI contains recommendations for SAT regimens and dosing, and includes recommendations for lower dosages for some antimicrobials, but are mostly based on expert opinion. [4] (Table 1)

Table 1. Proposed SAT treatments for periprosthetic infections of shoulder arthroplasty

Microorganism	Preferred SAT Treatment	Alternative SAT Treatment[a]	Notes
Cutibacterium acnes	Penicillin V 500 mg PO bid to qid, or Amoxicillin 500 mg PO tid or Cephalexin 500 mg PO tid or qid	Minocycline or doxycycline 100 mg PO bid	Suggested reduced doses are amoxicillin 500mg bid, Pheneticillin 500 mg qid, or doxycycline 100mg qd[b]
Staphylococci, methicillin-susceptible	Dicloxacillin 500 mg PO tid or qid, Or Cephalexin 500 mg PO tid or qid, Or Cefadroxil 500 mg PO bid	Clindamycin 300 mg PO qid or Amoxicillin-clavulanate 625 mg PO tid	Rifampicin in combination is not recommended for SAT
Staphylococci, methicillin-resistant	Cotrimoxazole 960mg PO bid or Minocycline or doxycycline 100 mg PO bid	Clindamycin 300mg qid or 450mg tid	- linezolid should not be used for chronic suppression. - suggested reduced doses are cotrimoxazole 960mg qd or 480mg bid, clindamycin 300mg bid or tid, clindamycin 600mg bid, or doxycycline 100mg qd[b]
β-haemolytic streptococci	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid	
Enterococcus spp, penicillin susceptible	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid		Doxycycline and pristinamycin are alternatives if isolate susceptible. Linezolid should not be used for chronic suppression.
Gram-negative organisms	Ciprofloxacin 250–500 mg PO bid, or Cotrimoxazole 1 DS tab PO bid		Consider beta-lactam as an alternative if susceptible

[a] If patient allergic or intolerant to, or organisms resistant to, the preferred regimen

[b] Hanssen JLJ, van der Wal RJP, van der Linden HMJ, van Prehn J, Scheper H, de Boer MGJ. Dosing and treatment duration of suppressive antimicrobial therapy in orthopedic implant infections: a cohort study. J Bone Jt Infect. 2024 Jun 4;9(3):149-159. doi: 10.5194/jbji-9-149-2024. PMID: 38903857; PMCID: PMC11187703.

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