Review Article

Prolonged antibiotic suppression therapy for infected hip and knee arthroplasty: is this a viable option?

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Abstract: Antibiotics form the mainstay of treatment of prosthetic joint infection (PJI) irrespective of the surgical approach used. As the population ages and the level of comorbidities increase in patients presenting for total hip and knee arthroplasty surgery, there will be a cohort of patients for whom surgical intervention is not the optimal approach. There are also those who will refuse surgical intervention. For these groups management with prolonged suppressive antibiotic therapy (PSAT) is a potential option. There is a relative paucity of literature examining this modality. The aim of this paper is to present a contemporary review of this management approach, identify the populations where this option is indicated and discuss the benefits and risks of this approach. Modern studies report the success of PSAT between 66–83% when preceded by surgery. Risk factors for failure of PSAT can be divided into local (e.g., multiple previous surgeries), host (e.g. immunocompromised) and microbial (e.g., *Staphylococcus aureus infecting organism*). With lifelong therapy, antibiotic side effects may be as common as 40% but several authors report no serious adverse events when antibiotics are appropriately selected. The duration of antibiotics after any PJI surgery is controversial. Current evidence suggests antibiotic therapy after a debridement and implant retention should be lifelong. There may be a subgroup of patients who can stop antibiotics and remain in remission but it is currently not possible to accurately select these patients.

Keywords: Prolonged suppressive antibiotic therapy (PSAT); prosthetic joint infection (PJI); hip; knee; revision

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Introduction: what is prolonged suppressive antibiotic therapy (PSAT) and when do we use it?

The incidence of hip and knee arthroplasty is increasing annually (1). Prosthetic joint infection (PJI) is responsible for 14.8% of revision total hip arthroplasty procedures and 25.2% of all revision knee arthroplasty procedures (2). PJI is one of the most challenging complications due to the difficulty, cost and morbidity associated with treatment. Two-stage revision is considered the gold-standard (3). Single stage revision remains a popular option which is gaining popularity (3,4). For acute post-operative or acute haematogenous infections, debridement, and implant retention (DAIR) with exchange of modular components is also widely used but success rates vary considerably (5). If strategies to salvage the joint fail, final surgical options include excision arthroplasty, arthrodesis, or amputation (3).

Irrespective of the surgical approach used, antibiotics have a central role in the management of PJI. The optimal antibiotic duration in the treatment of PJI is also controversial (6). Common practice after the surgical aspect of management is performed is for 4–6 weeks of intravenous (IV) therapy followed by 4–6 weeks oral (PO) antibiotics (7).

Several terms have been coined for longer term administration of antibiotics including PSAT and antibiotic suppression therapy (AST). PSAT can be defined as the administration of antibiotics for an extended period, potentially lifelong, to prevent episodes of sepsis arising from the joint; improve symptoms and prevent or prolong progression to further surgery. It can be used as a sole treatment for the patient who is not surgically fit or declines surgery. More commonly, it is used as a surgical adjunct when risk factors for failure are present, such as virulent or resistant organisms, multiple joint infections, failed revisions for infection, immunosuppression or removal of all or part of the prosthesis is not technically feasible or if a patient refuses surgery (7).

The decision to use this strategy is based on having a defined organism and sensitivity profile; a safe oral antibiotic and a system to facilitate close follow up and monitoring of the patient in the community. In practice, PSAT is most commonly used following a DAIR procedure with several retrospective series documenting outcomes in this group (5,8,9). Less commonly it is also used after single-stage, two-stage or even as a first line therapy (6,7,10).

This article discusses the success rate of PSAT, the factors that influence its success and failure and reviews the evidence on the optimal duration.

The success of PSAT: what does the current literature say?

The success of PSAT varies considerably in the literature from 8-86% but studies are heterogenous in both their methods and patient populations (6,7,11-13).

Success in these studies is often defined as the absence of symptoms from the affected joint. Failure is most commonly defined by progression to further surgery, episodes of sepsis, or progressive pain.

Early studies report very poor outcomes with PSAT. Johnson and Bannister reported early results from the United Kingdom (11). Twenty-five patients with infected TKA's received PSAT as the first line treatment and only two (8%) had resolution of pain and discharge after 1.3 years (mean) antibiotic therapy. Goulet *et al.* (12) reported 19 cases of hip PJI. Eight received PSAT as a first line treatment, whilst 11 received incision and drainage followed by PSAT. After 4.1 mean year follow up, only 9 (47%) were considered successfully managed. Tsukayama *et al.* (13) reported 8 knee and 5 hip PJI. All patients received debridement and implant retention and 4–6 weeks of IV antibiotic therapy followed by long term oral antibiotics. Only 23% patients were successfully managed using this technique after a mean 3.1 year follow up.

Contemporary results have varied from these early reports, however. Segreti *et al.* reported 78% success of DAIR followed by PSAT in 6 hips and 12 knees at 4.1 years mean antibiotic duration (8). Rao *et al.* reported similar success in 2003 with 86% infection free survival of 36 patients at a mean 4.4 years of antibiotic suppression (9). This was a heterogenous group of joints, including 19 knees, 15 hips and two elbows, although all patients received DAIR and modular component exchange and 4–6 weeks of IV antibiotics before commencing PSAT. Over half the patients in the study had symptoms for more than 30 days and were still managed with DAIR.

All published PSAT studies to date are observational and largely retrospective. Only Siqueira *et al.* include a control group (7). In their study of both hip and knee PJI, treated by either DAIR with modular exchange or two-stage revision, they report 68.5% infection free survival at 5 years. In contrast, a matched cohort who did not receive PSAT following DAIR or two-stage revision had only 41.1% infection free survival at 5 years. Ninety-two patients were in the PSAT arm and received antibiotics on an individualized basis ranging from 6 to 165 months (mean 5.3 years), with those in the control arm receiving less than 6 months of antibiotics.

In the largest retrospective series to date, Weston *et al.* (14) reviewed 134 total knee arthroplasties (TKAs) all managed with DAIR and modular component exchange where possible, 6 weeks of IV antibiotics and PSAT for the life of the implant. After a mean 5 year follow up, 66% of implants were infection free. The authors also report a 34% death rate at mean 3.6 years, a finding not commonly documented in other studies.

Two recent studies also demonstrate positive outcomes in patients who received PSAT as first line therapy without surgery. Wouthuyzen-Bakker *et al.* (10) reported 67% success in their series of 21 hips, knees and shoulders. Sandiford *et al.* (6) observed 83% success in a series of 23 hips and knees. Five and three patients in each study respectively received PSAT as first line therapy, and only one failure was observed. This is in keeping with Prendki *et al.*, who found that 29 of 38 patients who received PSAT as first line therapy were event free at 2 years. All patients in this cohort were over 80 years of age and 10/38 (26%) were deceased at the time of final follow up (15).

Bryan *et al.* (2017) reported 90 total hip or hemiarthroplasties which underwent DAIR, IV antibiotics for 6 weeks then oral for the life of the implant. Success was 83% at a mean 6 years and 34% of patients deceased at final follow up (16). Pradier *et al.* (17) studied 78 patients who had infected knee, hip, elbow and shoulder arthroplasties and were treated with lifelong doxycycline or minocycline. The success rate at mean 2.8 year follow up was 72%. Three-quarters (75.6%) of patients received a DAIR prior to PSAT and the remainder received either single- or two-stage exchange.

These studies suggest that PSAT can be a successful technique to control recurrence of infection and episodes of sepsis without further surgical intervention. However, a 14–34% failure rate is still observed in the larger, more recent studies and it is therefore key to identify factors which might contribute to this (9,14).

Risk factors for failure of PSAT

These can be broadly divided into local factors, host factors and microbial factors.

Local factors

TKAs have a potentially higher risk of developing PJI than hip arthroplasty (18). Some authors have also suggested that PJI involving the knee is more likely to fail PSAT therapy. Siqueira *et al.* (7) found three times the risk of reinfection with PSAT in knees compared with hips. Likewise, Pradier *et al.* found significantly fewer hips failed PSAT and Sandiford et al's failures (4/25) occurred exclusively in knee prostheses.

Sinus tracts are poor prognostic indicators in PJI and are considered to be an indication for two-stage exchange, the current gold standard. Prendki *et al.* included these patients in their cohort (24%) and confirmed with univariate analysis an increased risk of failure in this subset (15).

Megaprostheses may be associated with higher risk of PSAT failure but requires further study with larger numbers. In the series by Wouthuyzen-Bakker *et al.* (10) (10 megaprostheses, 21 joints), megaprostheses were associated with a 40% reduction in implant survivorship. This was not observed by the senior author with one treatment failure in a megaprosthesis secondary to Candida albicans (5 megaprostheses, 25 joints) (6).

A higher number of previous surgeries on the joint can also influence the outcome of PJI-surgery. This is multifactorial, resulting from reduced bone stock, soft tissue loss, repeated exposure opportunities and the selection of harder-to-treat, resistant organisms. Byren *et al.* reported 3.1 times the risk of failure with multiple previous surgeries (5).

Host factors

Previous studies have highlighted higher failure rates in immunocompromised patients, specifically those with rheumatoid arthritis (11,19). For this reason, immunocompromised patients are over-represented in PSAT studies as they are deemed high risk of relapse. In the series by Pradier *et al.* 46.1% of patients were immunosuppressed and 20.5% had neoplasia but 71.8% success was observed at 2.8 years illustrating that PSAT therapy might still have benefit in this cohort (17). Hypoalbuminaemia may also be associated with increased risk of failure (15). McPherson *et al.* in 2002 (20) grouped many risk factors into a staging system that has shown to be clinically correlated with death, amputation, and implant retention. Bryan *et al.* found McPherson's host grading system to correlate well with treatment failure. Bryan *et al.* reported 8%, 16% and 44% failure rates for PSAT in McPherson A,B and C patients respectively (16).

Patient age is controversial. Prendki *et al.* (15) found patients aged over 85 at increased risk of failure, whilst Weston *et al.* (14) report a higher failure rate in younger patients (hazard ratio 2.4). The authors argue young age provides more time to fail. Body mass index (BMI) and gender have not yet been shown to influence outcomes in PSAT (14).

Microbial factors

Staphylococcal species have been implicated in up to 72% of all cases of PJI (12,17).

Staphylococcus aureus (S. aureus) has been associated with reduced implant survivorship by up to 33%, increased the rate of failure by 3.6 and implant removal by 3.2 times (14). All failures in the study by Rao *et al.* (9) were due to Staphylococcus spp. Similarly, Byren *et al.* reported a 2.9 times increased risk of failure of PSAT if Staph. aureus was the infecting organism (5).

Fungal PJI is typically managed by two-stage revision as these pathogens are atypical and more difficult to eradicate. Only two studies report outcomes from PSAT in candida infection. Rao *et al.* (9) successfully managed one case with DAIR and modular component exchange, followed by 35 months of fluconazole. We observed persistent wound discharge in a patient managed by single stage revision and IV caspofungin for 6 weeks followed by oral fluconazole and clotrimazole. More data is required in this small subset of patients to determine their prognosis with PSAT (6).

The timing of presentation of PJI has not been shown to influence the results of patients treated with PSAT. No difference in failure rates has been reported between acute haematogenous and acute post-operative infections treated with DAIR and PSAT (14).

Precautions with PSAT: antibiotic side effects

Administering antibiotics for the life of an implant may reduce the rate of infection recurrence but does expose the patient to side effects associated with antibiotic use. Current studies are heterogenous in the types of antibiotics used. This likely reflects the heterogenous mix of pathogens responsible. Side effects have been reported and often result in a change in antibiotic agent. Wouthuyzen-Bakker *et al.* and Tsukayama *et al.* (10,13) found 43% and 38% of patients respectively required a change of antibiotic for this reason. Other authors report lower incidences. Pradier *et al.* (17) document 18% rate of adverse events but only 8% of patients resultantly discontinuing therapy. Rao *et al.* (9) reported that 8% of patients suffered antibiotic side effects consisting mainly of diarrhoea.

Serious events are rare. In an elderly cohort aged over 80, Prendki (15) reported a single case of recurrent Clostridium difficile colitis. Several authors have reported no significant complications with the use of appropriately selected targeted antibiotic therapy (6,10,13).

Duration of PSAT

Most authors have observed that a small number of patients stop antibiotics prematurely due to side effects or through their own volition. A proportion of these patients who stop their therapy remain symptom free at follow up. This raises the question of whether PSAT should be for the life of the implant, an extended period post-operatively or the commonly practised 3 months.

Byren *et al.* (5) proposed that extending antibiotic therapy may simply delay failure, rather than prevent it. In a cohort of 112 joints (92% hip and knee), they found stopping antibiotics increased the risk of infection recurrence by fourfold, with most occurring within 4 months of cessation. However, 13% of patients in this study had an arthroscopic washout and these accounted for 8/20 failures in the study. Moreover, 21% of patients had repeated DAIR procedures that by other study protocols would be judged a failure. Their definition of failure differed when compared to the majority of authors who have examined this subject.

Pradier *et al.* (17) found PSAT for the life of the implant had greater infection free survival than those in whom antibiotics had been discontinued at 2 years (failure 21.2% *vs.* 42.3%, P=0.05).

Siquera *et al.* (7) used six months as a minimum cut-off for defining PSAT, and found this increased implant survival rate from 41.1% to 68.5% after a DAIR but no statistically significant improvement was found for two-stage exchange. Bryan *et al.* (16) found 80% of failures occurred within 6 weeks of DAIR, whilst the patient was receiving intravenous antibiotics. Thereafter, chronic suppression reduced recurrence of infection from 11% to 3%. In Rao *et al.*'s series (9), 3/36 patients chose to stop antibiotics early after 6–12 months and all three remained asymptomatic. Two of 23 patient's in the senior author's series also discontinued stopped antibiotics after 1–1.5 years and were also asymptomatic at final follow up. Other authors have demonstrated that even with low-grade infection, cessation of antibiotic suppression can result in up to 30% of patients suffering recurrence of infection-related symptoms (5). Current evidence suggests PSAT combined with DAIR should be considered for the life of the implant rather than a finite, extended period. It is possible that some patients might be able to stop antibiotic therapy and remain in remission; however, there is currently insufficient information to accurately select these patients.

Conclusions

PSAT can be an effective treatment option, with success rates of 66–83% when preceded by surgery. Most studies are small and consist of heterogenous populations. This reflects that patients have to be carefully selected for this management option.

If the preceding surgery is a DAIR, antibiotics should be given for the life of the implant as current evidence suggests this can improve implant survivorship. Serious adverse events secondary to antibiotics are rare.

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