Suppressive Antibiotic Treatment in PJIs

Subjects: Orthopedics

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The treatment of prosthetic joint infections (PJIs) is a complex matter in which surgical, microbiological and pharmacological aspects must be integrated and, above all, placed in the context of each patient to make the best decision. Sometimes it is not possible to offer curative treatment of the infection, and in other cases, the probability that the surgery performed will be successful is considered very low.

Keywords: suppressive antibiotic treatment ; prosthetic joint infection ; prolonged antibiotic

1. Therapeutic Options for Prosthetic Joint Infections

The goal of treating a prosthetic joint infection (PJI) is to eradicate the infection and to maintain or regain implant function. This often involves the replacement of the prostheses, although in some cases (acute infections), the original implant can be salvaged through extensive debridement and prolonged antibiotic therapy, which is referred to as DAIR (debridement, antibiotics and implant retention) [1]. In the remaining situations, the cure can be obtained only by removing the implant, followed by the placement of a new prosthesis, either during the same surgical procedure (one-stage revision) or after a period with antibiotics (two-stage revision) [2]. However, reimplantation is sometimes not possible after removal (resection arthroplasty), and in rare situations, amputation may be necessary. Eventually, due to the patient's conditions or the anticipated sequelae of the intervention, a potentially curative surgical intervention is waived. In this scenario, orthopaedic surgeons turn their gaze to infectious disease (ID) consultants. Can antibiotic treatment help the patient?

2. Concept and Definition of Suppressive Antibiotic Treatment (SAT)

The term "suppressive antibiotic treatment" (SAT) refers to the administration of antibiotics in the long term or indefinitely over time. In the area of PJI, SAT is considered a "noncurative" strategy, in which antimicrobials are administered with the aim of reducing symptoms and delaying or preventing the progression of PJI that needs a surgical procedure to be cured that, for some reason, will not be performed (at least for a prolonged period of time). SAT can also be used in situations in which adequate surgical treatment is performed and the probability of cure is considered very low.

3. SAT Indications

SAT appears to be an infrequent therapeutic option in a series (5–14%) that reports the approach of patients with PJI [3][4][5]. However, in those patients over 80 years of age, the percentage treated by SAT can reach 36.5% [6].

SAT is intended to reduce local symptoms (presence of a sinus tract, inflammation, pain, etc.) and thus delay or elude a surgical intervention that has been rejected or is intended to be avoided. It is possible that SAT may delay or prevent prosthetic loosening by reducing the local peri-implant inflammatory process, although no studies have evaluated this potential effect. Additionally, SAT can be considered a general benefit for the patient's health as a result of the reduction in persistent chronic inflammation [7].

In summary, SAT can be considered for patients with acute PJI for whom conservative treatment (DAIR) has failed, or for patients with chronic-late PJI whose implants are not going to be removed or replaced due to any of the following circumstances:

- Unacceptable anticipated functional results.
- Surgical sequelae (or risks) disproportionate to the symptoms.
- Presence of another disease or condition that makes it advisable to substantially delay the intervention.

- Short life expectancy.
- Major surgical contraindication.
- Patient’s refusal of the intervention.

These situations would therefore be considered PJI with “certain” treatment failure. This would mean that there is evidence of PJI with no curative treatment planned.

There are other situations in which the probability of failure of surgical-medical treatment can be anticipated to be high, although not certain [8][9]. Here, we would cite the following scenarios:

- Chronic PJI managed with partial replacement of components.
- Early PJI managed with DAIR and high risk of failure (or potential serious consequences thereof), such as immunosuppressed patients on chemotherapy, patients managed by arthroscopic debridement and/or without replacement of modular components, and cases with suboptimal antimicrobial therapy (multidrug-resistant organisms).
- Multiple previous failures of treatment of PJI

Once the indications are established, certain conditions are required to be able to carry out SAT:

- Known aetiology (not essential but lack of knowledge clearly hinders decision-making).
- Possibility of monitoring and clinical control of adherence and toxicity.
- Availability of orally active antibiotics against the causal aetiological agent (although, as we will see later, there may be alternatives).

4. Evidence on SAT Efficacy

4.1. Does SAT Truly Work? What Results Does It Offer?

Evidence of the efficacy of SAT is scarce. A cohort study in which patients with stable PJI (69% with implants for <90 days) were managed with implant retention and prolonged antibiotic therapy for more than 1 year showed that the failure rate (recurrence of infection or need for surgical revision) was four times higher in patients who discontinued antibiotic treatment [10]. Interestingly, most of the patients with discontinued treatment did not exhibit treatment failure, suggesting that many were actually cured. However, the higher rate of treatment failure in patients who stopped taking antibiotics indicates that, in this series, a proportion of patients not cured by DAIR benefited from continuing antibiotic treatment, via delayed or avoidance of failure, which occurred mostly in the first four months. Further arguments in favour of SAT efficacy are provided by the cases that were “rescued” through SAT after the failure of other strategies [10][11][12], as well as by the observation that some SAT failures were temporarily related to the suspension of antibiotic treatment [13].

The interpretation of SAT efficacy is very difficult for three reasons: the absence of controlled studies, the inclusion of patients with acute infections who would be cured by DAIR, and differences in the criteria for evaluating efficacy in published series (Table 1). For example, for some authors, the efficacy criterion was to avoid surgery (even if infection was not controlled) [3], while others required, in addition, control of the symptoms [4][9][11][14]. Success rates varied in the different series from 23% to 84%. However, the series with the highest success rates included patients with early PJI [4][9][14], many of whom would have had the same outcome with much shorter treatments.

Table 1. Published Series on SAT in PJI.

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Goulet, 1988 [3]	19	90% chronic 10% acute	*S. aureus* (21%), CoNS (21%), *Streptococcus* spp. (32%)	49.2	Retention of the implant	63%	No data
Tsukayama, 1991 [15]	13	100% chronic	*S. aureus*, (54%), CoNS (46%)	37.2	Retention of the implant	23%	38% antibiotic needed to be changed
Segreti, 1998 [4]	18	50% chronic 50% acute	*S. aureus* (44%), CoNS (44%)	48	Remained asymptomatic and functional prosthesis	83%	22% CDI
Rao, 2003 [14]	36	53% chronic 47% acute	*S. aureus* (26%), CoNS (50%)	60	Remained asymptomatic and functional prosthesis	86%	8% diarrhoea
Marculescu, 2006 [13]	88	No data	*S. aureus* (32%), CoNS (23%)	23.3	Absence of the following: Relapse, reinfection, presence of acute inflammation in the periprosthetic tissue or at any subsequent surgery on the joint, development of a sinus tract, death from prosthesis-related infection, or indeterminate clinical failure	57%	3% diarrhoea, 11% hypersensitivity, one case of CDI

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Byren, 2009 [9]	112	31% chronic 69% acute	*S. aureus* (40%), CoNS (23%)	27.6	Absence of the following: Recurrence, wound or sinus drainage recurring or persisting for 3 months beyond the index debridement procedure or requirement for revision surgery (irrespective of the indication)	82%	No data
Prendki, 2014 [6]	38	61% chronic 39% acute	*S. aureus* (39%), *Streptococcus* spp. (18%), Gram-negative bacilli (17%)	24	Absence of the following: Persisting infection, relapse, new infection, treatment discontinuation because of severe adverse events, or related or unrelated death	60%	1 case of recurrent CDI.

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Siqueira, 2015 [16]	92	61% chronic 39% acute	*S. aureus* (48%), CoNS (35%)	69.1	Absence of the following: Subsequent surgical intervention for infection after the index procedure, persistent sinus tract, drainage, or joint pain at the last follow-up visit, or death related to the PJI	69%	No data
Prendki, 2017 [10]	136	No data	*S. aureus* (62%), CoNS (21%)	24	Absence of the following: Local or systemic progression of the infection, death, or discontinuation because an adverse drug reaction	61%	18.4% discontinued antibiotics, but in half of cases, the antibiotic could be replaced by another.
Pradier, 2017 [8]	39	61% delayed or late 39% acute	*S. aureus* (79%), CoNS (10%)	24	Absence of the following: Signs of infection assessed ≥24 months after the end of the curative treatment and then at the last contact with the patient, or death related to the PJI	74%	15% (phototoxicity and gastrointestinal intolerance)

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Wouthuyzen-Bakker, 2017 [17]	21	62% late or delayed 38% early	*S. aureus* (33%), CoNS (38%)	21	Absence of the following: Pain during follow-up, surgical intervention is needed to control the infection, or death related to PJI	67%	43% reported side effects and needed change or adjustment of the dosage.
Pradier, 2018 [18]	78	60% delayed or late 40% early	*S. aureus* (40%), CoNS (32%)	34	Absence of the following: Signs of infection assessed ≥24 months after the end of the curative treatment and then at the last contact with the patient, or death related to the PJI	72%	18% phototoxicity and gastrointestinal disturbance
Escudero-Sánchez, 2019 [19]	302	73% chronic 11% haematogenous 16% early postoperative	*S. aureus* (31%), CoNS (33%)	36.5	Absence of the following: Appearance or persistence of a sinus tract, need for debridement or replacement of the prosthesis due to persistence of the infection, or the presence of uncontrolled symptoms, death related to PJI	59%	17% gastrointestinal 5% cutaneous

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Leijtens, 2019 [20]	23	30% early 70% late or delayed	*S. aureus* (2%), CoNS (61%)	33	Absence of the following: Reoperation for PJI or death related to PJI	56.5	24% needed change or dosage modifications.
Sandiford, 2019 [5]	24	No data	*S. aureus* (25%), CoNS (21%)	38.4	Absence of the following: Sepsis arising from the affected joint, no progression to further surgery, or death related to PJI.	83	4.2% rash 4.2% rifampicin interaction

CDI: Clostridioides difficile infection; CoNS: coagulase-negative staphylococci.

We found only one controlled study where patients with PJI at high risk of failure after surgery (DAIR or replacement) managed with SAT were compared with patients in the same conditions who were not managed with SAT. The cases were "matched" using a propensity score. Patients who received SAT had a better outcome at 5 years (68.5% free of infection) than those who did not receive SAT (41.1%) [16]. In a recent multicentre cohort that represents the largest series published to date, we estimated that SAT was effective (control of symptoms and no reintervention) in approximately 75% of the patients after two years and in 50% of patients at 5 years of follow-up [19]. Only patients with persistent infection from whom the implant was not removed were included in this cohort.

4.2. What Factors Are Associated with SAT Failure?

Few studies have analysed the factors associated with SAT failure. The failure rate seems higher among patients with a sinus tract and in those with infections caused by S. aureus [13][20][21][22].

In the multicentre study mentioned above, we investigated predictors of failure (defined as the persistence of uncontrolled symptoms of PJI, including sinus tract, or the need for further surgery for debridement or removal of the prosthesis due to infection) [19]. A multivariate analysis showed that the factors associated with failure were the following:

- Aetiology of infection other than Gram-positive cocci (essentially Gram-negative rods, fungi, or negative cultures). This could be explained because, in general, we have fewer orally active antimicrobials for Gram-negative bacilli.
- Location of the prosthesis in the upper limbs. It is difficult to explain this finding. In any case, the number of PJIs in the upper limbs was very low.
- Age less than 70 years. It seems paradoxical, but perhaps younger patients managed by SAT could be more often immunosuppressed or have “tumoural” prostheses, which has been associated with the worst prognosis [17].

In our opinion, at this moment, there are no firm or clear predictors of failure, which means that SAT should not be excluded if the patient meets the conditions mentioned above.

4.3. Why Could SAT Stop Working? Is the Development of Resistance Frequent?

In our previously cited cohort study, the coinvestigators were unable to attribute the failure to any specific cause in 52% of the cases. Among the known or attributable causes, the most frequent was the abandonment of treatment or poor

adherence (24% of all failures). The development of resistance was not a common cause, as it could only be invoked as a cause of failure in 12% of the cases. This observation has also been made by other authors [18]. In another 11% of patients, the cause of failure was the existence of a previously unsuspected pathogen in cultures that was not covered by the prescribed SAT [19].

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