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Ongoing suppression prevents relapse in streptococcal periprosthetic joint infection: A prospective long-term cohort study

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SUMMARY

Objectives: Antimicrobial suppression improves short-term outcome of streptococcal periprosthetic joint infection (PJI) compared to standard treatment. This study assesses the long-term effectiveness of suppression.
Methods: This prospective study included consecutive patients with streptococcal PJI. Infection-free survival was analyzed using the Kaplan-Meier method and compared between patients receiving standard therapy (12 weeks) and those with suppression therapy (> 6 months) with the log-rank test.
Results: A total of 63 PJI episodes were analyzed. Standard treatment was administered to 33 patients, while 30 patients received suppression therapy (10 had ongoing and 20 had discontinued suppression at time of follow-up). Predominant pathogens included Streptococcus agalactiae (n=20) and Streptococcus dysgalactiae (n=18). The main surgical procedures used were two-stage exchange (n=35) and prosthesis retention (n=21). At 7.5 years, infection-free survival was significantly higher in the suppression group (62%) compared to the standard therapy group (38%) (p=0.038). Streptococci accounted for 14 of 27 failures (52%). Suppression effectively prevented streptococcal infection during treatment; however, relapses or new streptococcal infections occurred in 5 of 20 patients (25%) after discontinuation. Failures during ongoing suppression were exclusively caused by gram-negative rods.
Conclusions: Suppression therapy significantly improves long-term outcome in streptococcal PJI. While suppression effectively prevents streptococcal reinfections during treatment, the risk of recurrence re-emerges after discontinuation.

Introduction

Streptococcal periprosthetic joint infection (PJI) is associated with higher failure rates compared to infections caused by other pathogens.[1–4] The reasons for this disparity remain unknown and may include the lack of antimicrobial agents with proven activity against streptococcal biofilms.[5,6] The treatment strategies for streptococcal PJI vary widely between institutions. While some centers practice antimicrobial suppression of various durations with different antibiotic agents and dosages, others adhere to a standard 12-week antimicrobial treatment regimen.

Previous research suggested that antimicrobial suppression therapy of six months or longer significantly improves outcomes in streptococcal PJI compared to the standard 12-week treatment.[2] However, critical questions remain unanswered, including the optimal duration of suppression, the most effective antibiotic and dosage, and the risks of relapse or reinfection after discontinuation of therapy. Moreover, the long-term effectiveness of antimicrobial suppression, particularly beyond two years of follow-up, has not been systematically studied. This is clinically important, as prolonged suppression carries risks such as adverse side effects and the development of antimicrobial resistance.[7–11]

This study aims to assess the long-term impact of antimicrobial suppression on streptococcal PJI, compare outcomes between ongoing and discontinued suppression, and identify patient subgroups that derive the greatest benefit from suppression. These findings will provide valuable insights to guide clinical decision-making in the management of this challenging condition.

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Patients and methods

Study population and design

This study is a follow-up to a previously published prospective observational cohort study of streptococcal PJI conducted from 2009 to 2018.[2] Additional patients treated between 2019 and 2021 were included and the long-term outcome was evaluated. The study included patients aged ≥18 years with a confirmed streptococcal PJI involving the hip, knee or shoulder joint. Exclusion criteria were early treatment failure within 12 weeks (including infection-related death), polymicrobial infections (presence of additional pathogen(s) other than streptococci), and follow-up periods of less than two years.

From 2009 to 2015, patients with streptococcal PJI were treated with a standard 12-week antimicrobial regimen. Starting in 2016, due to observed high treatment failure rates, antimicrobial suppression was implemented in all patients, irrespective of the route of infection (haematogenous or non-haematogenous), surgical approach (prosthesis retention or removal), streptococcal species, or antimicrobial susceptibility.

The study protocol was approved by the institutional ethical committee (EA1/040/14) and was conducted in accordance with the most recent version of the Declaration of Helsinki.

Definitions

Streptococcal PJI was diagnosed according to institutional criteria.[12] Of note, all included episodes were retrospectively classified as confirmed infections based on the European Bone and Joint Infection Society (EBJIS) definition criteria.[13] If streptococci were isolated in blood culture only, an additional non-microbiological criterion was required for the diagnosis of PJI, e.g., increased leukocyte count in synovial fluid, intraarticular purulence, a sinus tract communicating with the prosthesis, or a histopathology finding consistent with infection. The haematogenous route of infection was defined as previously reported.[14]

Treatment success was defined by the presence of all of the following criteria at the last follow-up: (i) infection-free status, characterized by a healed wound without sinus tract and/or discharge, and no signs of PJI recurrence, (ii) no further surgical intervention for persistent or perioperative infection, (iii) absence of PJI-related death within 3 months.

Surgical treatment

Surgical strategies were determined based on infection acuity, prosthesis stability and local findings by an interdisciplinary team of orthopedic surgeons and infectious diseases specialists experienced in the field of septic surgery. Acute infections were managed with debridement, mobile part exchange, and prosthesis retention, while chronic infections were addressed with one- or two-stage prosthesis exchange.

Antimicrobial treatment

Initial treatment included 1–4 weeks of intravenous antibiotics (depending on clinical response; until wound was healed and without discharge and serum C-reactive protein was low or normal), followed by oral amoxicillin (or in case of allergy to penicillin - doxycycline, clindamycin or levofloxacin). Suppression duration ranged from six months to several years, depending on antibiotic tolerability and patient preferences. For two-stage prosthesis exchanges, antibiotics were administered continuously until re-implantation in the prosthesis-free interval and resumed after re-implantation.

Follow-up evaluation

Patients were followed up at the outpatient clinic at 3, 6 and 12 months after revision surgery, and annually thereafter. The quality of life and side effects were assessed by using a standardized questionnaire. For patients unable to attend follow-up visits, standardized phone interview was conducted to assess treatment outcome and antimicrobial tolerability. Patients from the original cohort with successful short-term outcome were re-contacted via phone to evaluate the long-term follow-up and antimicrobial tolerability.

Statistical analysis

Categorical variables were compared using the Fisher's exact test, for comparison of continuous variables the Mann-Whitney-U test was applied. A two-sided p-value of < 0.05 was considered significant. The probability of event-free survival was estimated using the Kaplan-Meier survival method and survival curves between groups were compared by the log-rank Mantel-Cox test. An alpha level of 0.05 was considered significant.

Univariate analysis included previously identified factors influencing the treatment outcome,[2] such as antimicrobial suppression, history of revisions, prosthesis retention, involvement of knee prosthesis, S. *dysgalactiae* infection, and haematogenous infection route. These factors were also included in the multivariable logistic regression analysis. Odds ratios from multivariable analysis are presented in a Forest plot, stratified by the presence or absence of any risk factors for treatment failure. All statistical analyses and graphics were performed using Prism (version 9.3.1; GraphPad, La Jolla, CA, USA).

Results

Patient and infection characteristics

Among 93 patients with streptococcal PJI treated during the study period, 63 (68%) were included in this study. Thirty patients were excluded due to follow-up < 2 years (n=14), polymicrobial infections (n=12), and early failure within 12 weeks (n=4). Of included patients, 33 (52%) received standard 12-week antimicrobial regimen, while 30 (48%) were treated with antimicrobial suppression (Table 1). Most patients (n=43, 68%) had acute infections (< 4 weeks after last surgery or < 4 weeks of symptom duration), while the PJI of the remaining 20 patients (32%) were classified as chronic infections. Local and systemic clinical findings at admission are shown in Table 2.

Microbiological findings

Beta-hemolytic streptococci were isolated in 39 patients (62%), while viridans-group streptococci were identified in 25 patients (40%) (Table 3). One patient had a polymicrobial infection with four different strains of Streptococcus spp. (of both groups) in multiple samples. Notably, S. dysgalactiae was more frequent in the suppression group than in the standard treatment group. Blood cultures were positive in 6/14 (43%) episodes in the standard treatment group and 5/21 (24%) in the suppression group (p=0.283).

Treatment

Table 4 summarizes the surgical and antimicrobial treatment given to the investigated patients of both groups.

Surgical treatment

Retention of the prosthesis with exchange of mobile parts was performed in 21 patients (33%), all of whom had an acute PJI. Two-

Table 1
Patient demographics and infection characteristics of 63 streptococcal PJI.

Variable	All patients (n=63)	Patients with standard treatment (n=33)	Patients with suppression (n=30)	P value
Male sex	36 (57)	15 (45)	21 (70)	0.074
Median age (range) – years	70 (35–87)	71 (49–87)	70 (35–87)	0.881
Affected joint				
Knee	36 (57)	21 (64)	15 (50)	0.316
Hip	26 (41)	12 (36)	14 (47)	0.451
Shoulder	1 (1)	-	1 (3)	
Patients with previous revision surgery[a]	39 (62)	22 (67)	17 (57)	0.447
Haematogenous pathogenesis	44 (70)	21 (64)	23 (77)	0.287
Median time (range) from primary prosthesis implantation to PJI– years	5.4 (0.1–35.1)	5.4 (0.1–16.3)	5.3 (0.1–35.1)	0.110

NOTE. Data are no. (%) of patients, unless otherwise indicated.
[a] including 25 patients with septic revisions (11 with standard treatment and 14 with suppression) and 14 with aseptic revisions (11 with standard treatment and 3 with suppression). No information on pathogens of prior septic revisions available.

Table 2
Infection characteristics of 63 streptococcal PJI at admission.

Variable	All patients (n=63)	Patients with standard treatment (n=33)	Patients with suppression (n=30)	P value
Signs and symptoms				
Pain	57 (90)	28 (85)	29 (97)	0.199
Local signs	46 (73)	24 (73)	22 (73)	1.000
Sinus tract	9 (14)	5 (15)	4 (13)	1.000
Fever or rigors	24 (38)	11 (33)	13 (43)	0.787
Laboratory findings on admission				
Serum C-reactive protein				
Median (range) – mg/L	170 (3–468)	115 (3–393)	203 (26–468)	0.110
Increased (> 10 mg/L)	57/62 (92)	27/32 (84)	30 (100)	0.053
White blood cell count				
Median (range) – G/l	11.8 (5.2–31.0)	12.3 (5.2–31.0)	11.4 (5.4–22)	0.208
Increased (> 10 G/l)	37 (59)	20 (61)	17 (57)	0.802
Synovial fluid leukocyte count				
Increased (> 2000/ul or > 70% granulocytes)	29/30 (97)	8/9 (89)	21/21 (100)	0.300
Median absolute count (range) – /µl	70,600 (1,400–352,800)	92,600 (1,400–336,200)	56,900 (2,100–352,800)	0.529

NOTE. Data are no. (%) of patients, unless otherwise indicated. Where the denominator is shown, data was not available for all patients.

Table 3
Microbiology findings of 63 streptococcal PJI.

Variable	All patients[a] (n=63)	Patients with standard treatment[a] (n=33)	Patients with suppression (n=30)	P value
Beta-hemolytic streptococci	39	18	21	0.299
S. agalactiae	20	14	6	0.064
S. dysgalactiae	18	3	15	0.001
S. pyogenes	1	1	-	1.000
Viridans group streptococci	27	18	9	0.198
S. mitis/oralis	13	10	3	0.061
S. gallolyticus	3	2	1	1.000
S. (para)sanguinis	2	-	2	0.223
S. gordonii	3	3	-	0.240
S. anginosus	3	1	2	0.601
S. thermophilus	1	1	-	1.000
	1	1	-	1.000
S. salivarius	1	1	-	1.000
S. mutans	1	-	1	0.476

NOTE. Data are no. (%) of patients.
[a] One patient in the standard treatment group had a polymicrobial infection with four different streptococci of both groups. Therefore, the sum exceeds the number of 63 and 33, respectively.

stage prosthesis exchange was the most common surgical approach (n=35, 56%), with similar prosthesis-free intervals in both groups (median 69 days, range 42–182 days). One-stage exchanges were performed in three patients, and four underwent prosthesis removal without replacement.

Antimicrobial treatment

Data on antimicrobial treatment were available for all but one patient. The median duration of intravenous treatment was 21 days (range 7–102 days), with combination regimens more frequently used in the suppression group (77%) compared to standard treatment group (35%) (p=0.002).

Among 60 patients receiving oral antibiotics (30 in the standard group and 30 in the suppression group), 44 (73%) received monotherapy, while 16 (27%) received combination therapy, mostly with rifampin. Amoxicillin was the primary agent used for suppression in 28/30 patients (93%), while alternatives such as clindamycin and doxycycline were employed in case of penicillin allergy (one patient each).

In the suppression group, 10 patients were on ongoing therapy at follow-up (median duration 42 months, range 25–91 months), while

Table 4
Surgical and antimicrobial treatment of 63 streptococcal PJI.

	All patients (n=63)	Patients with standard treatment (n=33)	Patients with suppression (n=30)	P value
Surgical treatment				
Prosthesis retention[a]	21 (33)	8 (24)	13 (43)	0.120
One-stage exchange	3 (5)	2 (6)	1 (3)	1.000
Multi-stage exchange[b]	35 (56)	20 (61)	15 (50)	0.453
Median implant-free interval (range) – days	69 (42–182)	71 (42–182)	51 (44–162)	0.442
Prosthesis removal	4 (6)	3 (9)	1 (3)	0.614
Antimicrobial treatment[a]				
Initial intravenous antibiotics				
Median duration (range) – days	21 (7–102)	21 (7–102)	19 (7–98)	0.752
Penicillin derivative	47/62 (76)	25/32 (78)	22 (73)	0.770
Cephalosporine	12/62 (19)	4/32 (13)	8 (27)	0.206
Clindamycin	2/62 (3)	2/32 (6)		0.492
None	1/60 (2)	1/32 (3)		1.000
Combination treatment	34/61 (56)	11/31 (35)	23 (77)	0.002
with gentamicin	16 (47)	6 (55)	10 (43)	
with other antibiotic[c]	18 (53)	5 (45)	13 (57)	
Oral treatment	60/62 (97)	30/32 (94)	30 (100)	0.493
Median duration[d] (range) – weeks	23 (2–364)	7.5 (2–16)	56.5 (30–364)	< 0.001
Combination treatment with Rifampin	20/60 (33)	14/30 (47)	6 (20)	0.054

NOTE. Data are no. (%) of patients, unless otherwise indicated. Where the denominator is shown, data was not available for all patients.
[a] For one patient in the standard treatment group no data on antibiotic treatment was available.
[b] Including 23 patients with two-stage exchange and 12 patients with more than two (range 3–5) surgeries.
[c] Combination with fosfomycin (n=10) or vancomycin (n=8).
[d] After the last operation.

20 had discontinued suppression (median duration 13 months, range 8–39 months). Discontinuation reasons included physician discretion (n=14), patient preference (n=4), or advice from a general practitioner (n=2).

Outcome evaluation

The median follow-up was 3.9 years (range 0.3–13.3 years), with infection-free survival rate of 38% for standard treatment and 62% for suppression at 7.5 years (p=0.038, Fig. 1). Overall success was achieved in 36/63 patients (57%), with significantly higher rates in the suppression group (22 of 30 patients, 73%) compared to the standard group (14 of 33 patients, 42%) (p=0.021). Among those receiving suppression, success rates were comparable between ongoing (80%) and discontinued therapy (70%) (p=0.682).

Microbiology of failure cases

Fig. 2 shows the different success rates according to failure pathogen stratified by antimicrobial therapy strategies. Ongoing suppression effectively prevented failure due to any Streptococcus species. However, two failures occurred during suppression, and both were caused by gram-negative rods (Escherichia coli and Pseudomonas aeruginosa, respectively, Table 5).

In the group of patients who had stopped the suppression treatment, two patients experienced relapse with the original pathogen (S. agalactiae and S. dysgalactiae, respectively), more than

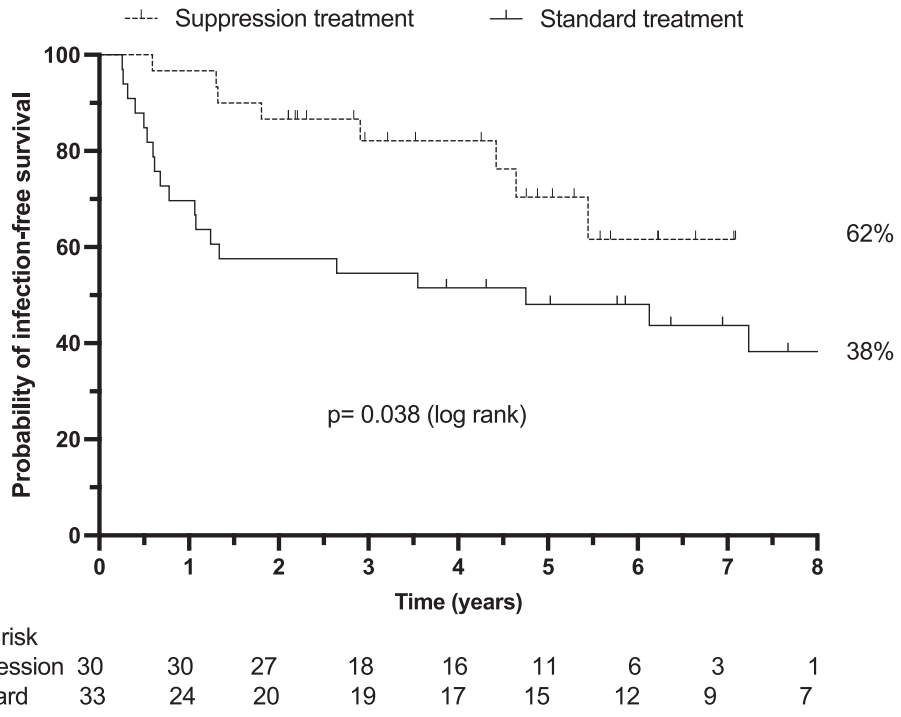

Fig. 1. Kaplan-Meier analysis of infection free survival of patients with standard treatment and suppression. After 8 years, no further failure occurred.

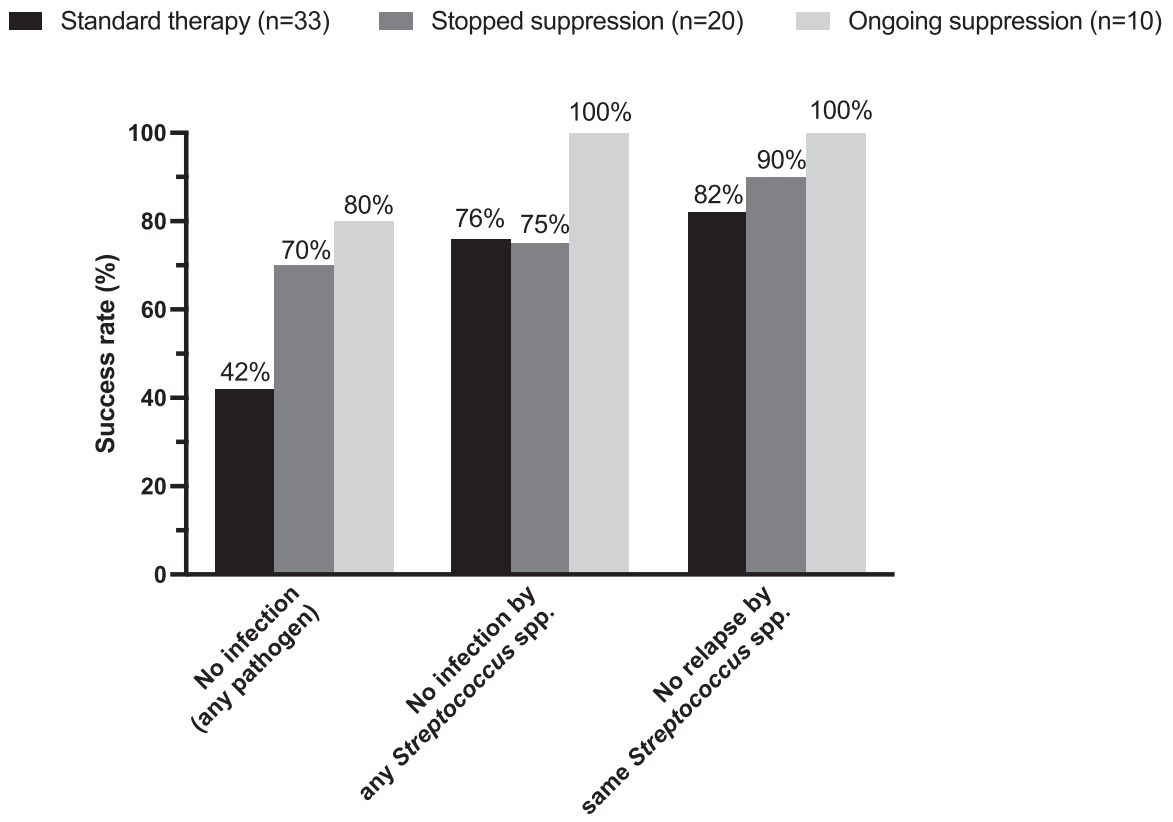

Fig. 2. Different success rates according to antimicrobial treatment strategies with regards to pathogen causing failure.

Table 5
Characteristics of episodes failing under/after suppression.

	Index PJI				Suppression				Failure	
	Joint	Pathogen	Pathogenesis	Surgical treatment	Suppression antibiotic	Continuing at time of failure	Duration (weeks)	Interval from stopping to failure (weeks)	Pathogenesis	Pathogen
1	Knee	S. dysgalactiae	Haematogenous	Multistage exchange	Amoxicillin	No	64	13	Haematogenous	S. agalactiae
2	Knee	S. mitis/oralis	Contiguous	Multistage exchange	Amoxicillin	No	45	186	Unknown	Unknown
3	Knee	Milleri group Streptococcus	Haematogenous	Multistage exchange	Amoxicillin	Yes	274	-	Haematogenous	E. coli
4	Knee	S. dysgalactiae	Haematogenous	Multistage exchange	Amoxicillin	Yes	192	-	Unknown	P. aeruginosa
5	Hip	S. agalactiae	Haematogenous	Prosthesis retention	Amoxicillin	No	52	102	Unknown	S. agalactiae
6	Hip	S. dysgalactiae	Haematogenous	Prosthesis retention	Amoxicillin, changed to Doxycycline	No	52	18	Haematogenous	S. anginosus
7	Knee	S. parasanguinis	Haematogenous	Multistage exchange	Amoxicillin	No	52	4	Haematogenous	S. dysgalactiae
8	Hip	S. dysgalactiae	Haematogenous	Prosthesis retention	Amoxicillin, changed to Clindamycin	No	34	118	Persistence	S. dysgalactiae

two years after discontinuation of antimicrobials. Three patients (15%) experienced a failure due to another Streptococcus species after cessation of the suppression, and in one patient, the pathogen of failure remained unknown as the failure management took place in another hospital.

In the standard treatment group, 6 patients experienced a relapse with the same streptococcal species and 2 patients had a new infection with another Streptococcus species. Six failures were caused by another non-streptococcal pathogen, including coagulase-negative staphylococci (n=3), Staphylococcus aureus (n=1), Escherichia coli (n=1) and polymicrobial infection (n=1) caused by methicillin-resistant S. aureus, S. dysgalactiae and Enterobacter cloacae. In four of the failures, cultures were negative, and in one failure, the pathogen remained unidentified as the treatment was administered at another institution.

Pathogenesis of failure

Ten failures (37%) were persistence of infection (90% in the non-suppression group), 7 (26%) were caused by haematogenous spread (all caused by new pathogens), 5 (19%) were new postoperative infections and in 5 (19%) failures the pathogenesis was unknown.

Subgroup analysis

Success rates with suppression were higher than standard treatment across various subgroups (Fig. 3). Patients with prior revisions showed significantly better outcomes with suppression compared to standard treatment (76% vs. 36%, p=0.023). Suppression was particularly effective in cases caused by S. dysgalactiae (success rate 73% with vs. 0% without suppression, p=0.043). Trends favoring suppression were also observed in non-haematogenous PJI (success

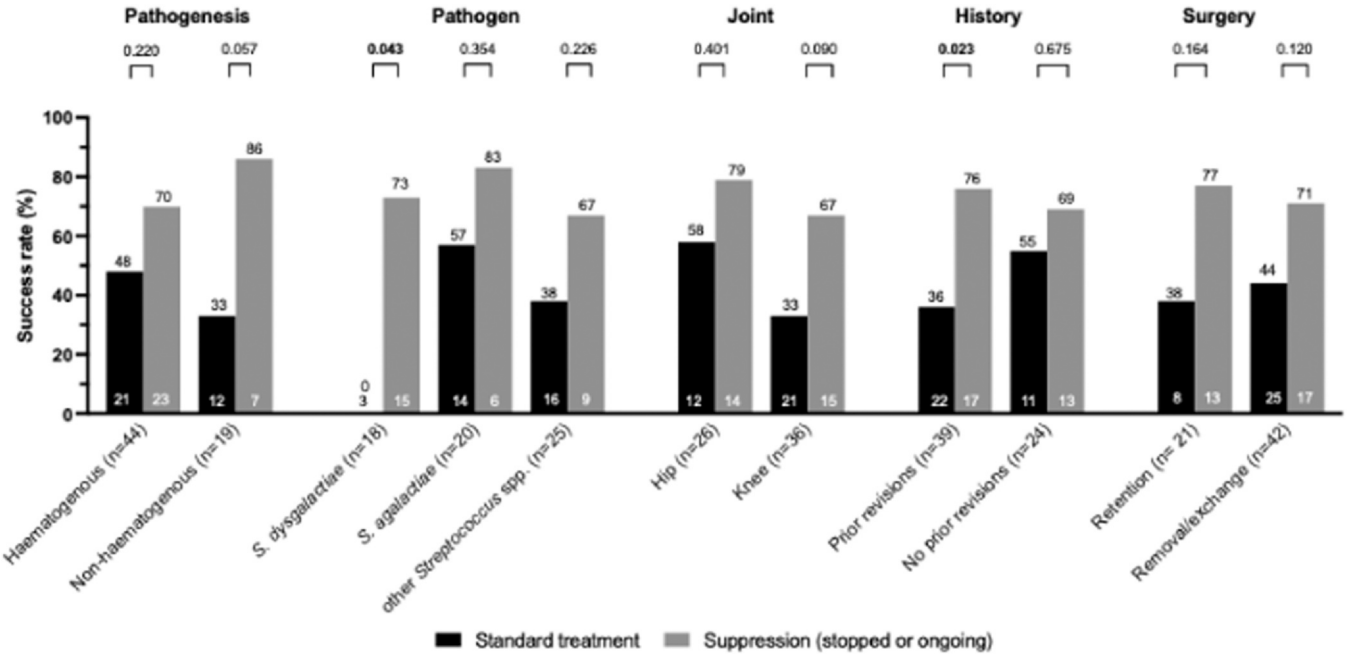

Fig. 3. Analysis of success rate (i.e., infection-free status) of standard treatment vs. suppression in subgroups according to factors characterizing PJI episodes and their treatment, and antimicrobial treatment strategies.

rate 86% vs. 33%) and in knee PJI (success rate 67% vs. 33%), though these differences did not reach statistical significance.

Haematogenous route of infection, infection caused by S. dysgalactiae, infected knee prosthesis, treatment strategy with retention of the prosthesis and a history with previous revisions were not significantly associated with failure in the univariate analysis, which lies in contrast to the protective effect of suppression (OR 0.27, 95% CI 0.09–0.76, p=0.015; see Supplementary Table). In multivariate analysis, antimicrobial suppression remained a significant factor improving the outcome in streptococcal PJI after correcting for the above-mentioned factors (OR 0.22, 95% CI 0.05–0.76, p=0.023, Fig. 4).

Tolerability of antimicrobial suppression treatment

Tolerability of antimicrobial suppression was evaluable in 23 patients. Of these, 10 (43%) reported side effects, primarily gastrointestinal symptoms (n=6, including nausea and diarrhea). Two cases of Clostridioides difficile enterocolitis occurred during amoxicillin (n=1) and clindamycin (n=1) therapy. The second most common side effect was allergic reactions (5 patients, all with drug-induced exanthema). Four patients had multiple side effects. Five patients with suppression with amoxicillin required antibiotic change due to side effects, either to doxycycline (n=4) or to clindamycin (n=1). Despite these issues, only 4 patients (17%) reported compromised quality of life due to suppression therapy.

Discussion

This study reinforces previous findings demonstrating that antimicrobial suppression therapy significantly improves outcome in streptococcal PJI compared to standard therapy. Specifically, suppression therapy maintained its protective effect over a median follow-up of 3.9 years and was the only independent factor associated with improved outcome in multivariate analysis, supporting the observations made in the previous short-term evaluation.[2]

In the aforementioned study, the outcome with suppression compared to standard treatment was significantly better (95% vs 53%) after a median of 13 months of follow-up.[2] Only one of 21 patients with suppression experienced failure that occurred two months after discontinuation of a 12-month suppression and was caused by another Streptococcus species. In contrast, 15 failures were documented in 32 patients with standard treatment and were caused by the same (n=7), new (n=4) or unknown (n=4) pathogen. The study provided the background for the suggestion of using

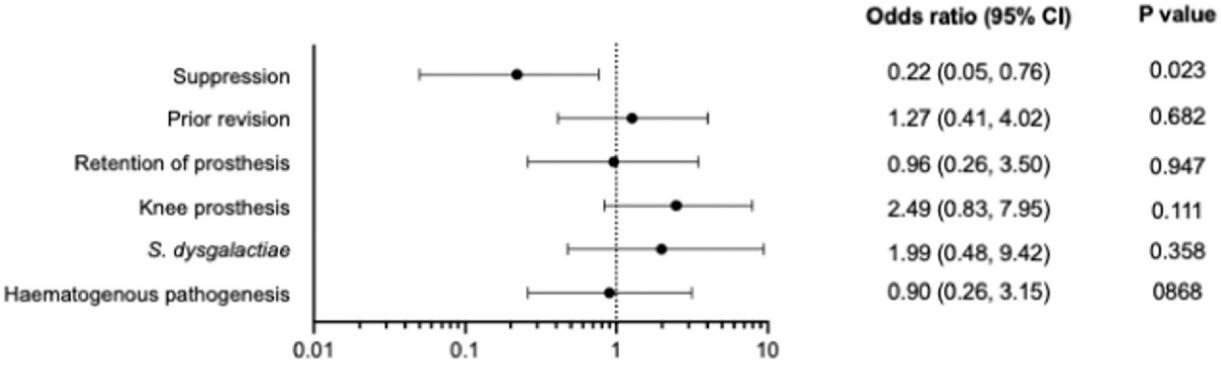

Fig. 4. Forest plot of possible risk factors for failure.

suppression in streptococcal PJI. However, it remains unclear whether suppression can be stopped at some point and if all or only particular subgroups of patients with PJI caused by streptococci benefit from prolonged antimicrobial treatment.

The high recurrence risk after stopping suppression remains concerning. Nearly one third of failures were caused by the same pathogen as the initial PJI episode, demonstrating the high persistence or recurrence rate in PJI caused by streptococci, as previously reported.[1] Approximately one quarter of patients who discontinued suppression experienced failure due to the same or another streptococcal species, underscoring the potential predisposition of certain hosts to (recurrent) streptococcal infections. However, ongoing suppression effectively prevented failures caused by Streptococcus spp., albeit at the cost of potential failures due to other pathogens, particularly gram-negative bacteria. One of those failures was again caused by a haematogenous spread on the prosthesis, while in the other case the haematogenous origin of Pseudomonas was suspected but formally could not be confirmed.

The majority of streptococcal PJIs occur after haematogenous spread from a distant focus[2] and haematogenous PJIs have previously been demonstrated to have worse outcome compared to non-haematogenous infections, irrespective of the causing microorganisms.[15] The biological mechanism how suppression prevents reinfection or relapses remains unclear. It may suppress or eliminate streptococci on the prosthesis surface, or it may counteract the individuals' susceptibility to streptococcal PJI by preventing a new haematogenous spread onto the prosthesis from a distant streptococcal infection. The observation, that all failures due to haematogenous spread were caused by a different, new pathogen excludes the assumption that a persistent distant focus caused the failure. This fact rather suggests a host-mediated predisposition to haematogenous PJI. It is unknown whether the reinfection rates after treatment of haematogenous infections can be reduced with antimicrobial suppression.

Whether suppression should be given indefinitely or can be discontinued at some point is of utmost clinical relevance and is discussed controversially.[16] While the difference of success rates in patients with and without suppression was significant in this study, it was minor when comparing patients who had stopped or continued suppression. The overall success rate in patients who had discontinued the suppression was lower by 10% compared to patients with ongoing suppression (70% vs 80%). However, the risk to experience another streptococcal infection after cessation was considerably higher than with ongoing suppression (25% vs 0%).

Our results suggest that patients with prior revisions (septic or aseptic) benefit most from suppression therapy. This is in line with a recent study evaluating suppression therapy after debridement and implant retention.[17] In addition, the beneficial effect of suppression only reached significance level in PJI caused by Streptococcus dysgalactiae (Fig. 3), which was associated with the poorest outcome among Streptococcus species in our study on short-term outcome.[2] However, in multivariate analysis Streptococcus dysgalactiae was not identified as risk factor for failure in the present study. Additionally, there was a tendency for higher success rate with suppression in non-haematogenous PJI (not in haematogenous PJI) and knee infections (not in hip infections). Nevertheless, due to the small sample sizes, the subgroup analysis might be underpowered and should be interpreted with caution.

Some authors have suggested suppression therapy as an option when patients refuse or are at high risk for surgical treatment.[18] In our cohort, antimicrobial therapy was given in combination with surgical treatment in all cases. Streptococcal infections are commonly of haematogenous origin with an acute fulminant course. In patients presenting in a septic state and with a high intraarticular bacterial burden, both immediate surgical and antimicrobial treatment are required to control the infection. Suppression without surgery would only be considered in chronic cases. However, the risk of failure without preceding mechanical reduction of bacteria and compromised tissue is high, with the additional risk of development of antimicrobial resistance, if antimicrobial treatment is given in this setting.

While suppression therapy demonstrates clear benefits, it is not without challenges. In our study, 43% of patients reported adverse effects, primarily gastrointestinal symptoms and allergic reactions. This is a higher percentage than previously reported.[8,19–21] Though largely mild, these effects impacted quality of life in fewer than 20% of cases. Furthermore, long-term use of antibiotics may foster resistant pathogens, as evidenced by suppression-related failures involving gram-negative bacteria. Apart from the side effects, selection of resistant pathogens and alteration of the microbiota should be investigated with long term suppression.[22] Furthermore, the use of intramuscular depot injection of penicillin, may be an alternative to oral application to overcome gastrointestinal side effects, in analogy to prevention of recurrent erysipelas. However, data on intramuscular administration of antimicrobials for the treatment of PJI is lacking.

While the results of this study support the administration of suppression in streptococcal PJI, the ideal duration remains unclear and needs further investigation. In our center, we administer antimicrobial suppression for at least 6 months, see the patient on a regular basis and reevaluate the duration of suppression individually, considering the previous history regarding the prosthesis, comorbidities, patients' preferences and tolerability of the antimicrobial agent. In this cohort, one patient has been receiving suppression for more than 5 years, because of a history of five previous streptococcal PJI episodes involving a megaprosthesis of the hip and knee with limited possibilities to treat another failure. During the suppression, no infection relapse or side effect occurred.

This study has some limitations. Firstly, the observational design with a sequential change of treatment strategy might pose a bias, as most patients in the non-suppression group were treated earlier, when general knowledge about PJI management was poorer than it was in the last years. Secondly, the small sample size of patients might mitigate relevant differences in the subgroup analysis. Nevertheless, the homogenous approach in this monocentric study outweighs the heterogeneity of international multicenter studies, especially considering the diverse approach to suppression therapy worldwide.[16,23] Moreover, we have not explored various host factors predisposing to streptococcal PJI. A better understanding of mechanisms of suppression could guide tailored treatment strategies in the future and should be further investigated.

In conclusion, antimicrobial suppression therapy offers significant long-term benefits in the management of streptococcal PJI, with ongoing suppression effectively preventing relapses and reinfections. However, discontinuation poses a recurrence risk, especially for streptococcal pathogens. Balancing the therapy's benefits against its side effects and potential complications requires a nuanced, patient-centered approach. The incidence of side effects is high, yet they are mild and rarely affect the quality of life of patients. Further research is essential to optimize its duration and explore its role across different patient populations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106437.

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