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Long-term antimicrobial suppression prevents treatment failure of streptococcal periprosthetic joint infection

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SUMMARY

Objectives: To evaluate the effect of oral antimicrobial suppression on the outcome of streptococcal periprosthetic joint infection (PJI).

Methods: Consecutive patients with streptococcal PJI receiving antimicrobial suppression for >6 months were prospectively included and compared to a retrospective control group without suppression. Outcome was assessed with Kaplan-Meier analysis and compared by the log-rank Mantel-Cox test. Multivariate analysis was used to identify factors associated with treatment failure.

Results: Of 69 streptococcal PJI episodes (37 knee, 31 hip and one shoulder PJI), 43 (62%) were caused by beta-hemolytic streptococci and 26 (38%) by viridans group streptococci. Debridement and prosthesis retention was performed in 27 (39%), one-stage exchange in 5 (7%), multi-stage exchange in 31 (44%) and prosthesis removal in 6 patients (9%). 24 patients (35%) were treated with antimicrobial suppression receiving oral amoxicillin ($n=22$), doxycycline ($n=1$) or clindamycin ($n=1$). After a median follow-up of 13 months (range, 0.5–111 months), 38 of 65 patients (58%) were infection-free. Suppressive antimicrobial treatment was associated with higher success rate compared with no suppression (93% vs. 57%, $p=0.002$), representing the only significant independent factor preventing treatment failure.

Conclusions: Long-term antimicrobial suppression was associated with significantly better treatment outcome and should be strongly considered in streptococcal PJI.

Introduction

Streptococci cause between 4% and 16% of periprosthetic joint infections (PJI), the majority of which occur through hematogenous spread originating from a distant focus such as oral cavity, heart valves, skin and soft tissue, genitourinary or intestinal tract.[1–4] The reported treatment success of streptococcal PJI varies from 58–71%[5–7] up to 83–94%.[8–10] The wide range may reflect various definitions of success used by different authors, impeding direct comparison of these studies. For instance, some authors considered infection caused by a different pathogen as treatment failure whereas others did not, reporting higher success rates.

Furthermore, antimicrobial treatment recommendations for streptococcal PJI vary widely, particularly regarding the type, dose and duration of antibiotic treatment. No consensus exists regarding the role of rifampin in streptococcal biofilm infections. Whereas findings of two retrospective cohort studies suggested better outcome by adding rifampin to the standard antibiotic regimens,[5,7] in vitro biofilm experiments[11] and another clinical study showed no beneficial effect.[6] Thus, the role of rifampin in streptococcal PJI remains controversial.

Another issue of debate in streptococcal PJI is the role of long-term antimicrobial suppression. Suppressive therapy is defined as prolonged oral antibiotic therapy to suppress symptoms of infection when cure is not expected or possible. It is often administered to patients not qualifying for surgery or refusing it, in patients with poor general prognosis or in palliative settings.[12,13] Due to treatment failure rates in streptococcal PJI exceeding 40% (both with and without adding rifampin),[6] long-term antimicrobial suppression was introduced in the treatment protocol at our institution and its outcome was prospectively assessed. We report the influence of various factors on the outcome of streptococcal PJI, including the impact of long-term oral antimicrobial suppression.

Patients and methods

Study design

This is a prospective cohort study (2016–2018) with a historical control group (2009–2015). It was conducted in a tertiary health-

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care center, providing advanced specialty care to a population of approximately four million inhabitants. The involved orthopedic department has an interdisciplinary septic surgical unit that takes care of about 300 patients with musculoskeletal infections per year. From 2009 to 2015, patients with streptococcal PJI received 6–12 weeks of antibiotic treatment. In January 2016, long-term oral antimicrobial suppression for ≥6 months was introduced. Oral amoxicillin was used as the first-line suppressive antibiotic, substitute drugs were doxycycline or clindamycin (depending on antimicrobial susceptibility, tolerance and allergy).

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

Study population

Consecutive patients with streptococcal PJI treated at our institution between July 2009 and August 2018 were included. Patients with incomplete data sets or polymicrobial PJI were excluded. Patients were identified from the institutional PJI registry. Parts of the data of some patients included in this study's first period who were treated without antimicrobial suppression have been published recently.[6]

Definitions

Streptococcal PJI was diagnosed based on the definition criteria recently proposed to the European Bone and Joint Infection Society (EBJIS) (currently being revised).[14] According to these definition criteria, PJI was diagnosed by presence of one or more of the following criteria: (i) macroscopically visible purulence, (ii) sinus tract communicating with the prosthesis, (iii) abnormal synovial fluid leukocyte count and differential (>2000 leukocytes/µl or >70% granulocytes), (iv) growth of *Streptococcus* spp. in synovial fluid, periprosthetic tissue or sonication fluid, (v) positive histopathology, defined as >23 granulocytes per 10 high-power fields, i.e. type II or type III periprosthetic membrane. If *Streptococcus* species grew in blood culture only, at least one additional non-microbiological criterion for the diagnosis of PJI was required.

PJI was classified according to its temporal appearance after surgery as early (<3 months), delayed (3–24 months) and late infection (>24 months). The hematogenous origin was defined if (i) the onset of symptoms was acute after an uneventful period after implantation and clinical examination, patient history and/or blood culture confirmed a direct relation to a distant focus or (ii) the same *Streptococcus* species that were isolated from the joint grew in blood cultures or from cultures of a distant infectious focus.

Acute infection was defined by newly onset symptoms lasting ≤4 weeks, including early perioperative PJI or late hematogenous PJI after an initially uneventful course after arthroplasty and without signs of prosthesis loosening at the time of symptom onset. PJI occurring after 4 weeks of surgery or presenting with a symptom duration of longer than 4 weeks were considered *chronic infection*.

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

Surgical treatment

Surgeries were performed by a dedicated team of septic orthopaedic surgeons, following institutional guidelines. In general, patients with an acute (early postoperative or late hematogenous) infection with symptoms lasting ≤4 weeks were treated with retention of the prosthesis, change of the mobile parts and meticulous debridement. Patients with chronic PJI, with signs of infection lasting >4 weeks or with a loosened implant were treated with one-stage or two-stage revision (long or short prosthesis-free interval), depending on the local soft tissue and bone conditions and the revision history.

Antimicrobial treatment

The empiric intravenous antibiotic treatment was switched to targeted treatment according to the type and antimicrobial susceptibility of the pathogen. The intravenous treatment was typically changed to oral 2–4 weeks after surgery. In case of a two-stage prosthesis exchange, antibiotics were continued until re-implantation without an antibiotic-free interval.

Follow-up evaluation

Patients were followed up in the outpatient clinic 3, 6 and 12 months after revision surgery, followed by annual visits. Clinical, laboratory and radiological evaluation was performed and interpreted interdisciplinarily by an orthopedic surgeon and an infectious disease physician. If patients did not appear for the follow-up visit, the evaluation was performed by phone interview using a standardized case report form.

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 and 95% confidence interval were estimated using the Kaplan–Meier survival method. Survival curves between groups were compared by the log-rank Mantel–Cox test. An alpha level of 0.05 was considered significant. Univariate regression analysis was used to determine the predictors of treatment failure, followed by a multiple logistic regression model (including the factors suppression, retention of prosthesis, duration of intravenous antibiotics, addition of rifampin, previous revision surgery and type of prosthesis). The selected variables showed significant difference in baseline characteristics or are subject of current debate in the scientific literature. Odds ratios from multivariable analyses are presented in Forest plots, stratified by the presence or absence of any risk factors for treatment failure. Statistical analyses and graphics were performed using Stata 15.1 (Stata Corp, College Station, TX, USA) and Prism (version 7.03; GraphPad, La Jolla, CA, USA).

Results

Patient data

Of 112 screened patients, 32 were excluded because of mixed infections and 11 because of missing data. Of the included 69 patients with streptococcal PJI, 24 (35%) were treated with antimicrobial suppression. Patient and prosthesis data are shown in Table 1. The pathogenesis was hematogenous spread in 49 (71%), perioperative colonization in 12 (17%), contiguous spread in 2 patients (3%) and unknown in 6 patients (9%). Thirty-nine patients (57%) underwent at least one revision surgery prior to occurrence of the actual PJI episode (range, 1–11 interventions), with significantly more patients with previous revision in the group without suppression treatment.

Table 1
Patient demographics and infection characteristics of 69 streptococcal PJI.

Variable	All patients ($n=69$)	Patients without suppression ($n=45$)	Patients with suppression ($n=24$)
Male sex	40 (58)	23 (51)	17 (71)
Median age (range), years	72 (47–92)	72 (47–92)	71 (49–91)
Affected joint			
Knee	37 (54)	25 (56)	12 (50)
Hip	31 (45)	20 (44)	11 (46)
Shoulder	1 (1)	–	1 (4)
Patients with previous revision surgery	39 (57)	30 (67)	9 (38)
Hematogenous pathogenesis	49 (71)	30 (67)	19 (79)
Temporal appearance			
Early	12 (17)	9 (20)	3 (13)
Delayed	27 (39)	17 (38)	10 (42)
Late	30 (43)	19 (42)	11 (46)
Time from primary prosthesis implantation to PJI, median (range) – years	5.7 (0.1–34.6)	6.3 (0.1–34.2)	4.7 (0.1–34.6)
Acute manifestation of PJI	51 (74)	31 (69)	20 (83)

Note. Data are no. (%) of patients, unless otherwise indicated.

Table 2
Infection characteristics of 69 streptococcal PJI at admission.

Variable	All patients ($n=69$)	Patients without suppression ($n=45$)	Patients with suppression ($n=24$)
Signs and symptoms			
Loosening	9/67 (13)	8/44 (18)	1/23 (4)
Pain	65 (94)	42(93)	23 (96)
Local signs	51 (74)	34 (76)	17 (71)
Sinus tract	11 (16)	9 (20)	2 (8)
Fever or rigors	27 (39)	17 (38)	10 (42)
Laboratory findings on admission			
Serum C-reactive protein			
Median (range) - mg/L	161 (3–468)	128 (3–393)	193 (36–468)
Increased (>10 mg/L)	62/67 (92)	38/43 (88)	24 (100)
White blood cell count			
Median (range) – G/l	11.9 (5.2–31.0)	12.3 (5.2–31.0)	10.0 (5.4–19.3)
Increased (>10 G/l)	35/68 (51)	24/44 (55)	11 (46)
Synovial fluid leukocyte count			
Increased (>2000/ul or >70% granulocytes)	32/33 (97)	12/13 (92)	20/20 (100)
Median absolute count (range) - 10^3/nl	133.0 (1.4–352,8)	234.6 (1.4–336.2)	183.1 (25.3–352.8)
Histopathology consistent with infection	52/55 (95)	37/39 (95)	15/16 (94)

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

Infection characteristics

Signs, symptoms and laboratory findings at admission are shown in Table 2. The median C-reactive protein value was significantly higher in the patient group receiving suppressive treatment compared to patients receiving no suppression.

Microbiological findings

PJI were caused by beta-hemolytic streptococci in 43 patients (62%) and by viridans group streptococci in 26 patients (38%) (Table 3). In the suppression group, significantly more infections were caused by beta-hemolytic streptococci than by viridans-group streptococci (79% vs. 21%, p <0.001) whereas both groups were balanced in the non-suppression group (53% vs 47%, $p=0.674$). In PJI affecting the hip, beta-hemolytic streptococci were more frequently found than viridans group streptococci (71% vs. 29%, $p=0.002$), but the two streptococcal groups were balanced in knee PJI (beta-hemolytic streptococci in 54% vs. viridans group streptococci in 46%, $p=0.642$). At the time of surgery, four patients were receiving antibiotic treatment.

The primary source of periprosthetic joint infection

Fig. 1 shows the origin of streptococci, stratified for viridans group and beta-hemolytic streptococci. The most common source of streptococci was the surgical site, followed by a primary infection focus in the cardiovascular system, oral cavity, skin and soft tissue, and genitourinary tract.

Surgical treatment

Table 4 summarizes the surgical and antimicrobial treatment given to the investigated patients. In 31 patients (44%) exchange of the prosthesis was performed in at least two stages, with a median prosthesis-free interval of 79 days (range, 42–182 days). The prosthesis was retained in 27 patients (39%), all of whom had an acute infection (22 hematogenous, four early postoperative and one contiguous PJI). Significantly more patients in the suppression group than in the non-suppression group had their prosthesis retained (63% vs. 27%, $p=0.005$). In one patient no surgery was performed as she was not suitable for surgery due to septic shock and advanced age.

Antimicrobial treatment

All patients except one were treated with antibiotics, predominantly with intravenous penicillin derivatives during the initial phase (Table 4). In about half of the patients, an intravenous combination treatment was administered. The median duration of intravenous treatment was 20 days (range, 0–101 days). Among 61 patients receiving oral antibiotics, 36 (59%) received a single antibiotic and 25 (37%) received a rifampin combination. In 24 patients a suppressive treatment of ≥6 months (range, 6 months to

Table 3
Microbiology of 69 streptococcal PJI.

Variable	All patients ($n=69$)	Patients without suppression ($n=45$)	Patients with suppression ($n=24$)
Beta-hemolytic streptococci	43 (62)	24 (53)	19 (79)
S. agalactiae	23	17	6
S. dysgalactiae	19	7	12
S. canis	1	–	1
Viridans group streptococci	26 (38)	21 (47)	5 (21)
S. mitis/oralis	13	10	3
S. gallolyticus	4	4	–
S. (para)sanguinis	4	3	1
S. gordonii	2	2	–
S. anginosus	2	1	1
S. thermophilus	1	1	–
Source of pathogen isolation			
Joint specimen positive	66 (96)	43 (96)	23 (96)
Synovial fluid	59/66 (89)	39/44 (87)	20/22 (91)
Periprosthetic tissue[1]	59/68 (87)	41/44 (93)	18/24 (75)
Sonication fluid	29/38 (76)	15/21 (71)	14/17 (82)
Blood culture	17/37 (46)	12/22 (55)	5/15 (33)

Note. Data are no. (%) of patients, unless otherwise indicated. Where the denominator is shown, data was not available for all patients.
[1] Four patients had been receiving antibiotics before revision surgery.

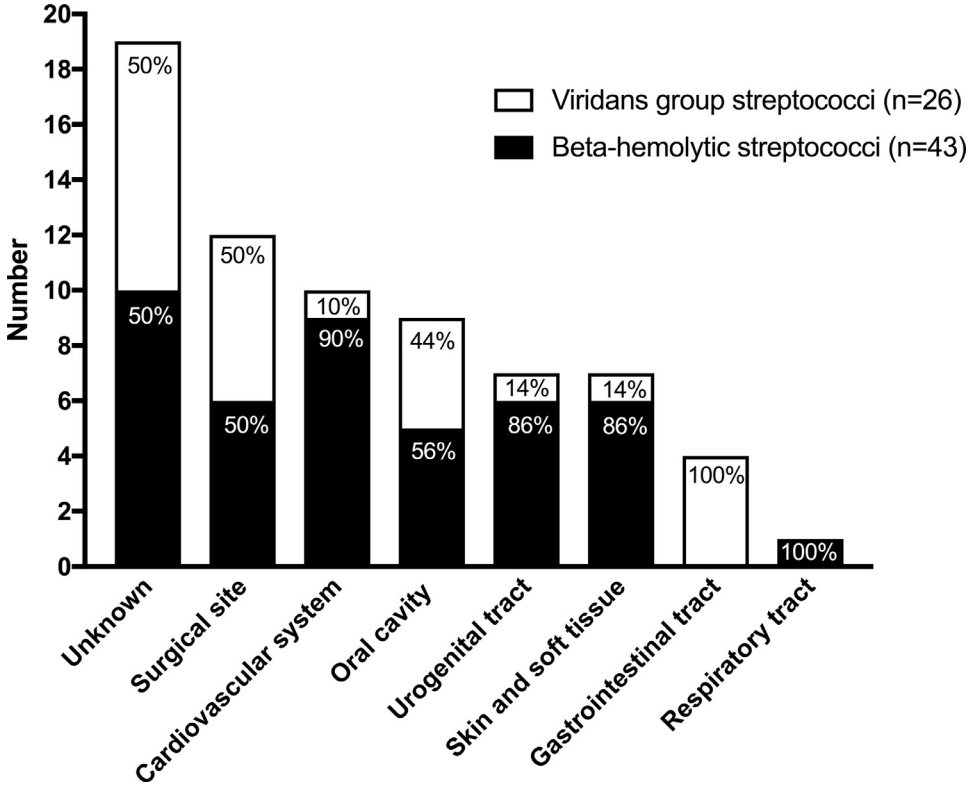

Fig. 1. The primary source of beta-hemolytic and viridans group streptococci.

lifelong) was initiated, among them 22 received amoxicillin, one doxycycline (because of a history of penicillin allergy) and one clindamycin (because of occurrence of rash during amoxicillin therapy). In 8 patients, suppressive treatment followed an initial 12-week rifampin combination regimen.

Outcome evaluation

Follow-up data was available for 65 patients (94%) who were included in the outcome analysis. Among evaluated patients, infection-free status was documented for 38 patients (58%) after a median follow up of 13 months (range, 0.5–111 months), with a median follow up of 26 months for the failure-free cases (1.5–110 months). Among the 27 failures, 12 showed a persistent infection due to same *Streptococcus* species, 11 experienced a new PJI caused by another pathogen, including *Streptococcus* species. other than initially isolated ($n=3$), *S. epidermidis* ($n=2$), *S. aureus* ($n=2$), gram-negative rods ($n=3$) or were culture-negative ($n=1$); four patients died related to streptococcal infection. Infection-free survival using Kaplan-Meier analysis for different *Streptococcus* species is shown in Fig. 2. No differences in outcome were observed between PJI caused by *Streptococcus agalactiae, S. dysgalactiae* and viridans group streptococci ($p=0.104$). At follow-up of 36 months, failure-free outcome was seen in 74% of PJI caused by *S. agalactiae*, in 60% of PJI caused by viridans group streptococci and in 52% of

Table 4
Surgical and antimicrobial treatment of 69 streptococcal PJI.

	All patients ($n=69$)	Without suppression ($n=45$)	With suppression ($n=24$)	*P* value
Surgical treatment				
Retention[1]	27 (39)	12 (27)	15 (63)	0.005
One-stage exchange	5 (7)	3 (7)	2 (8)	1.000
Multi-stage exchange	31 (44)	24 (53)	7 (29)	0.076
Median interval (range) - days	79 (42–182)	73 (42–182)	62 (47–161)	0.219
Surgeries needed, median (range), No.	2 (2–5)	2 (2–5)	2 (2–4)	0.757
Prosthesis removal	6 (9)	6 (13)	–	0.085
Antimicrobial treatment[2]				
Basic intravenous antimicrobial agent				
Duration (median, range-days)	20 (0–101)	14 (0–101)	21 (6–70)	0.040
Penicillin derivative	57/68 (84)	38/44 (86)	19 (79)	0.500
Cephalosporine	6/68 (9)	1/44 (2)	5 (21)	0.018
Other[3]	4/68 (6)	4/44 (9)	–	0.289
None	1/68 (1)	1/44 (2)	–	1.000
Combination treatment	34/67 (51)	19/43 (44)	15 (63)	0.204
with gentamicin	19 (56)	9 (47)	10 (67)	
with other antimicrobial agent[4]	15 (44)	10 (53)	5 (33)	
Oral treatment	61/68 (90)	37/44 (84)	24 (100)	0.046
Monotherapy	36/61 (59)	18/37 (49)	18 (75)	0.062
Rifampin combination	25/61 (37)	19/37 (51)	6 (25)	0.294

Note. Data are no. (%) of patients, unless otherwise indicated. Where the denominator is shown, data was not available for all patients.
[1] Including no surgery in the non-suppression group ($n=1$).
[2] No data on antibiotic treatment was available for one patient in the retrospective comparison group.
[3] Including clindamycin ($n=1$), meropenem ($n=3$).
[4] Combination with vancomycin ($n=7$), daptomycin ($n=2$), fosfomycin ($n=5$), ciprofloxacin ($n=1$).

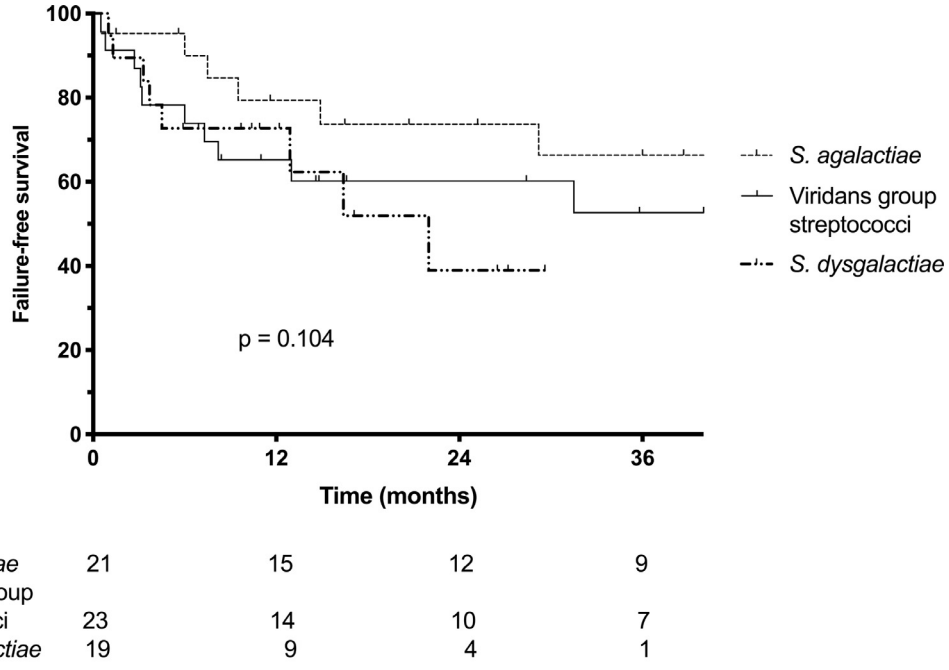

Fig. 2. Probability of infection-free survival stratified for the following groups: *Streptococcus agalactiae, S. dysgalactiae* and viridans group streptococci.

PJI due to *S. dysgalactiae*. Oral antimicrobial treatment with regimens including rifampin did not show better treatment success (12 of 45 patients, 48%) than without rifampin (23 of 34 patients, 68%) ($p=0.181$).

No differences were observed for the following factors in the univariate analysis: hematogenous vs. non-hematogenous PJI (29 of 46 [63%] vs. 9 of 19 [47%], $p=0.278$), hip vs. knee PJI (18 of 28 [64%] vs. 19 of 36 [53%], $p=0.447$), intravenous combination treatment vs. monotherapy (19 of 32 [59%] vs. 19 of 31 [61%], $p=1.000$), intravenous treatment of $\leq$14 days vs. intravenous treatment $>$14 days (16 of 28 [57%] vs. 21 of 35 [60%], $p=1.000$), beta-hemolytic vs. viridans group streptococci (26 of 42 [62%] vs. 12 of 23 [52%], $p=0.599$), bacteremia vs no bacteremia (9 of 16 [56%] vs. 15 of 19 [79%], $p=0.273$) and retention of the prosthesis vs. exchange of the prosthesis in acute infections (16 of 26 [62%] vs. 15 of 25 [60%], $p=1.000$). Only previous revision surgery before occurrence of streptococcal PJI was significantly associated with a poorer success rate than no previous revision surgery (18 of 38 [47%] vs. 20 of 27 [74%], $p=0.044$). After adjusting for surgical strategy (retention vs exchange/removal of prosthesis), duration of intravenous antibiotics, addition of rifampin, previous revision surgery and type of prosthesis, solely patients receiving suppressive treatment were less likely to experience treatment failure (OR 0.07, 95% CI 0.01–0.72) (Fig. 3).

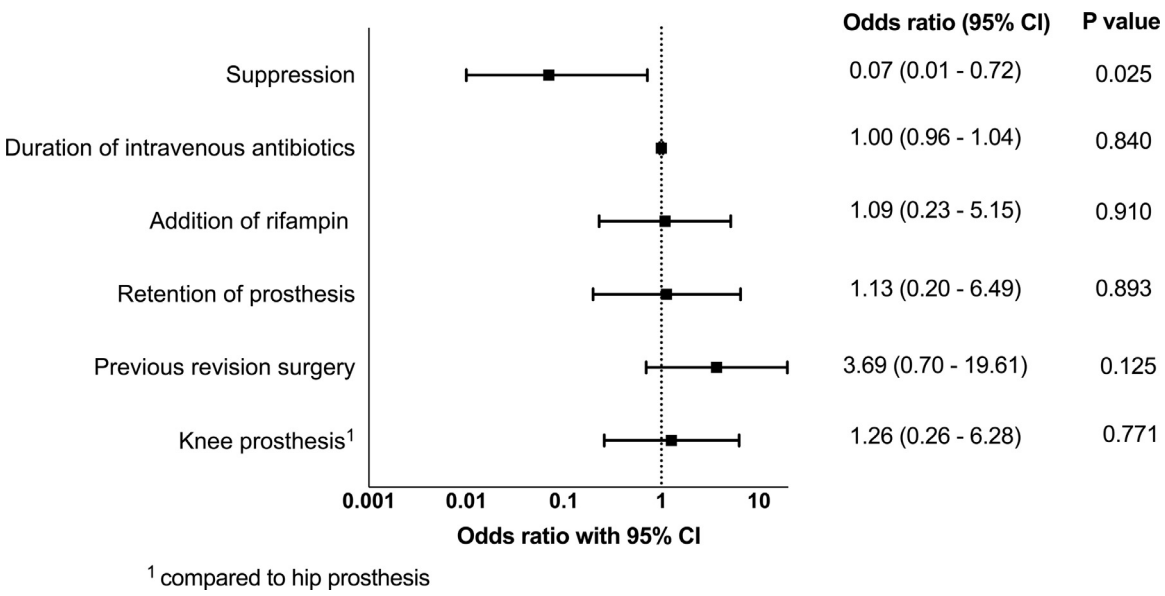

Fig. 3. Forest plot of possible risk factors for treatment failure.

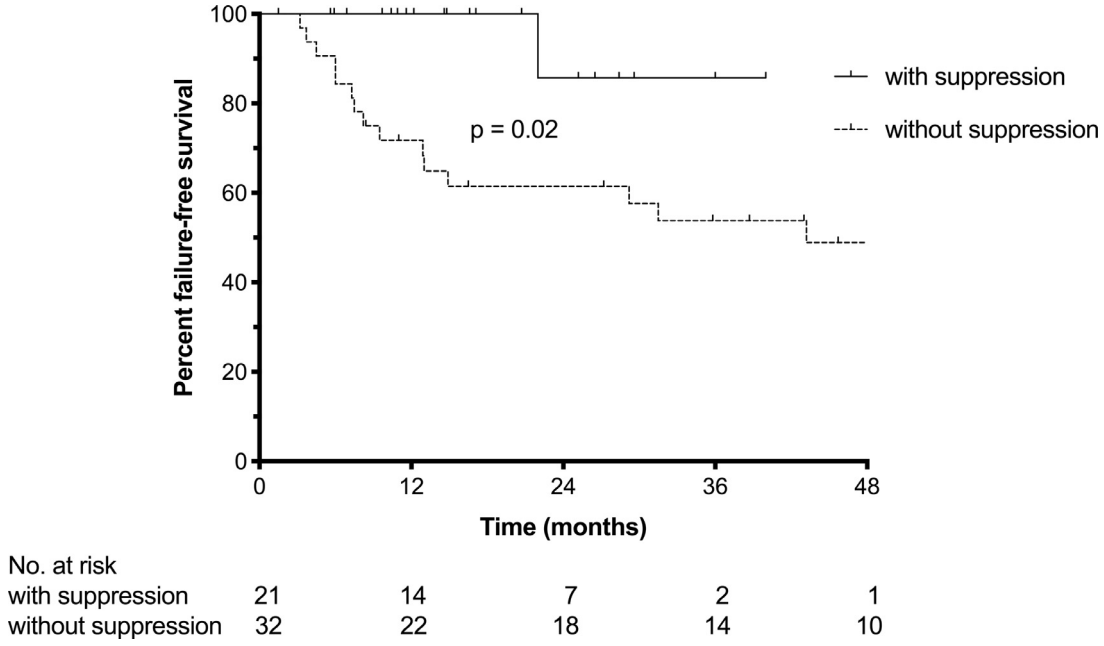

Fig. 4. Failure free survival analysis of patients who had not failed after 12 weeks of treatment.

Suppressive antimicrobial treatment

For the assessment of the effect of suppressive treatment, only patients who had not failed after 12 weeks were included. After exclusion of 12 patients with documented failure within this period, 53 patients remained for the outcome analysis. In the suppression group one patient of 21 failed (success rate, 95%), whereas in the comparison group without suppression 15 of 32 patients experienced a failure (success rate, 53%), demonstrating a significantly better outcome with suppression at last follow up ($p = 0.002$). Fig. 4 shows the Kaplan–Meier estimate of survival without failure of treatment. The probability of failure-free survival at 36 months was 86% for the suppression group and 54% for the comparison group ($p = 0.020$).

Table 5 shows the characteristics of all 16 failures that occurred after at least 12 weeks. Eleven patients receiving suppression were still under treatment at time of follow-up. The remaining patients without antibiotics at time of follow-up had stopped the antimicrobials for a median of 5 months (range, 2–24 months). The patient with failure receiving suppression for a hematogenous knee PJI caused by *S. dysgalactiae* (treated with exchange of the modular parts) failed two months after discontinuation of the one-year course of amoxicillin, experiencing again acute hematogenous PJI caused by *S. agalactiae*. No patient failed under treatment.

Four patients experienced allergic skin rash under antimicrobial suppression with amoxicillin and the treatment was consequently changed to doxycycline ($n = 2$) and clindamycin ($n = 2$). Two

Table 5
Characteristics of all failures, which occurred after 12 weeks (and were included in the comparison analysis); f, female; m, male; DAIR, débridement, antibiotics and implant retention.

Sex	Age	Joint	acute/ chronic	Pathogen	Surgical treatment	duration iv-treatment (days)	treatment duration (weeks)	Suppression planned	Oral antibiotics after last surgery	Failure type	Pathogen failure	Follow up (months)	Under antibiotics at follow-up?	interval after stopping antibiotics (months)
f	84	hip	acute	*S. mitis/oralis*	removal	28	4	no	none	persistence	unknown	43,2	no	42,2
m	73	hip	chronic	*S. mitis/oralis*	removal	14	6	no	rifampin combination	new infection	*S. aureus, S. dysgalactiae, Enterobacter* sp.	7,3	no	5,7
m	75	knee	acute	*S. dysgalactiae*	2-stage exchange	24	20	no	rifampin combination	death		4,5	no	0,5
m	65	knee	acute	*S. dysgalactiae*	2-stage exchange	70	78	yes	amoxicillin	new infection	*S. agalactiae*	22,0	no	3,1
m	61	knee	acute	*S. gordonii, S. mitis/oralis, S. pyogenes, S. salivarius*	DAIR	14	12	no	rifampin combination	persistence	unknown	13,0	no	10,0
f	67	knee	acute	*S. agalactiae*	DAIR	28	12	no	levofloxacin	persistence	*S. agalactiae*	6,0	no	3,0
f	66	hip	chronic	*S. agalactiae*	1-stage exchange	0	0	no	none	persistence	*S. agalactiae*	29,2	no	
m	67	hip	chronic	*S. anginosus*	removal	3	NA	no	none	persistence (death)	unknown	31,5	no	29,5
m	66	hip	acute	*S. agalactiae*	2-stage exchange	10	29	no	rifampin combination	persistence	*S. agalactiae*	9,5	no	1,9
m	53	knee	acute	*S. agalactiae*	2-stage exchange	7	12	no	ampicillin/ sulbactam	persistence	*S. agalactiae*	7,5	no	4,0
m	85	hip	acute	*S. dysgalactiae*	DAIR	14	14	no	rifampin combination	new infection	*S. epidermidis*	3,7	yes	–
m	60	knee	chronic	*S. agalactiae*	2-stage exchange	19	22	no	amoxicillin	new infection	*S. aureus*	14,9	no	9,7
f	84	knee	chronic	*S. mitis/oralis*	2-stage exchange	56	18	no	amoxicillin	persistence	*S. oralis/mitis*	8,2	no	4,0
f	71	knee	acute	*S. dysgalactiae*	2-stage exchange	28	10	no	ampicillin/sulbactam	persistence	*S. dysgalactiae*	12,9	no	9,5
m	75	knee	acute	*S. gallolyticus*	DAIR	20	12	no	rifampin combination	persistence	*S. gallolyticus*	3,2	no	0,4
m	75	knee	acute	*S. mitis/oralis*	2-stage exchange	25	12	no	rifampin combination	new infection	*S. gallolyticus*	6,0	no	2,4

patients receiving clindamycin experienced *Clostridioides difficile*–associated colitis.

Discussion

This study reveals some important characteristics of streptococcal PJI and corroborates their previously reported poor infection outcome.[5,6] Despite the high antimicrobial susceptibility of planktonic streptococci, eradication of this pathogen seems to be challenging in presence of a foreign body. Gonzalez-Moreno et al. reported interesting results from an in vitro study, in which eradication of streptococcal biofilms necessitated considerably higher concentrations (>125-fold higher) of all tested antibiotics as compared to eradication of planktonic bacteria. However, such high concentrations cannot be reached in clinical practice.[11] In that study, rifampin showed a synergistic effect only in combination with gentamicin, but not with other antibiotics. In line with this observation, the addition of rifampin was not associated with better treatment outcome in our study. This had previously been observed in a subgroup of the current cohort,[6] but it contradicts the results of two earlier trials that implied rifampin combinations were associated with significant higher cure rates.[5,7]

As a genuine novelty, this study provides a potential solution to decrease the high failure rate in streptococcal PJI. In our cohort, long-term oral antimicrobial suppression for at least 6 months was associated with significantly better outcome than no suppression (95% vs. 53%). The suppression group and the comparison group without suppression showed similar distributions regarding demographics and infection characteristics. In the suppression group, significantly more patients were treated with retention of the prosthesis and the intravenous treatment duration was longer. However, those two factors did not reach statistical significance when assessing potential factors influencing the outcome with univariate analysis. Six patients had their prosthesis removed (without reimplantation), none of them was treated with a suppression as the foreign material and hence the biofilm was completely removed.

Antimicrobial suppression was previously described as a salvage procedure in frail patients not qualifying for explantation of the prosthesis, in whom only debridement was performed.[15–17] Similarly, Everts et al. described four patients with successful outcome receiving suppression in PJI caused by streptococci.[18] However, in contrast to previous studies, we administered antimicrobial suppression to all consecutive patients with streptococcal PJI, not only to those for whom the treatment algorithm could not be followed due to inability to perform surgery.[19] Of interest, not only patients continuously receiving suppressive treatment were infection-free, but also patients who had discontinued suppression after several months. Many experts consider the need for suppressive therapy as criterion for treatment failure.[20] However, we applied the antimicrobial suppression in this study as measure to prevent treatment failure, keep the patients symptom-free and potentially eradicate the infection. Therefore, for the purpose of this study, antimicrobial suppression was not considered as treatment failure.

Suppressive treatment prevented “breakthrough” infections caused either by the original infecting organism or any new pathogen. This observation differs from experiences in infections in other medical fields requiring long-term antimicrobial suppression such as left ventricular assist device infections. A recent study reported clinical failure in nearly one third of patients treated with antimicrobial suppression.[21]

According to most reports, long-term antimicrobial suppression was well tolerated. Only in one study the long-term antimicrobial suppression showed limited clinical efficacy and had a substantial risk of adverse effects.[17] In our cohort, four patient experienced cutaneous rash after amoxicillin intake and were subsequently given another antibiotic (clindamycin or doxycycline). Two patients taking clindamycin developed *C. difficile*-associated colitis. Other patients tolerated the suppressive treatment well.

Contrary to previous reports,[22] in our study *S. agalactiae* were associated with a tendency to better outcome compared to viridans streptococci and *S. dysgalactiae*. For the latter, this observation may be explained by the virulence determinants of *S. dysgalactiae* that mimic those of *S. pyogenes*.[23,24]

As the majority of streptococcal PJI are of hematogenous origin, identification of the streptococci can guide further diagnostic work-up to identify and treat the potential primary source of infection.[2,4,8] Furthermore, recognition of acute-onset of hematogenous PJI allows for performance of debridement and retention of the prosthesis, despite the infection occurred late, i.e. several months to years after primary implantation.[8] Retention of the prosthesis represents an important advantage for the patient by using less invasive surgery, preventing loss of bone and soft tissue and reducing healthcare expenses, as compared to the two-stage-exchange.[3]

The majority of our patients was treated with penicillin derivatives, as recommended by the current guidelines.[19,25] Combination of two intravenous antibiotics in the initial treatment or prolonged intravenous treatment for >14 days was not associated with better treatment outcome.

There are several limitations of this study. First, it lacks the long-term follow-up of patients receiving suppressive treatment and approximately half of them were still on antibiotics. It is unknown whether the patients remain infection-free after discontinuation of suppressive treatment or relapses (or reinfections) may occur. In particular, this study cannot answer the question whether a prolonged suppressive treatment can “exhaust” streptococcal biofilm and thereby eradicate it. Therefore, it remains unclear which patients should receive antimicrobial suppression and for how long. Second, the control group without antimicrobial suppression was used from a retrospective cohort, i.e. before the introduction of the long-term suppression. The pragmatic use of a retrospective comparator introduces a potential bias, as management of PJI improved over time driven by the new scientific insights. Indeed, a randomized study would have a higher level of evidence. However, some relevant factors such as the surgical team, the applied surgical procedures and the complexity of the patient population remained similar throughout the study period. Therefore, the only identifiable difference was the introduction of the antimicrobial suppression.

In conclusion, the administration of long-term suppressive oral antimicrobial treatment was associated with significantly better outcome and should be strongly considered in streptococcal PJI, irrespective of the surgical treatment. The duration of the suppression remains unknown and needs to be determined in future randomized controlled trials.

Declaration of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.06.015.

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