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Group B streptococcus in prosthetic hip and knee joint-associated infections☆

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SUMMARY

The incidence of invasive group B streptococcus (GBS) infections in non-pregnant adults is increasing. Little is known about GBS in periprosthetic joint infections (PJIs). We aimed to analyse the clinical presentation of GBS PJI and its treatment in association with the outcome. The characteristics of 36 GBS PJIs collected from 10 centres were investigated. In 34 episodes, follow-up examination of ≥2 years was available, allowing treatment and outcome analysis. Most infections (75%) occurred ≥3 months after implantation. Most patients (91%) had at least one comorbidity; 69% presented with acute symptoms and 83% with damaged periprosthetic soft tissue. In 20 of 34 episodes debridement and retention of implant was attempted, but in five of these the prosthesis was ultimately removed. Hence, in 19 (56%) episodes, the implant was removed, including 14 immediate removals. In four episodes the removal was permanent. Penicillin derivatives and clindamycin were the most common antimicrobials administered (68%). In 94% the infection was cured, and in 82% functional mobility preserved. Debridement with implant retention was successful if the duration of symptoms was short, the prosthesis stable, and the tissue damage minor (10/10 vs 3/10 episodes, $P = 0.003$). Surgery that complied with a published algorithm was associated with a favourable outcome ($P = 0.049$).

Introduction

The incidence of invasive group B streptococcus (GBS) infections in non-pregnant adults has increased in recent years.[1] Age ≥65 years and chronic underlying conditions such as diabetes mellitus are associated with increased risk for invasive infections.[2] Elderly patients and those with such comorbidities represent an increasing segment of the population and many of them require joint arthroplasty. Little is known about the clinical presentation and management of GBS in periprosthetic joint infections (PJIs). Small case series have indicated immediate prosthesis removal as the treatment of choice, or have described failure rate ranging from 29% to 67% if retention of the implant was attempted.[3–6] However, other reports have described a high success rate in retaining the implant.[7,8] Another uncertainty in the treatment of GBS PJI is the medical therapy. The use of aminoglycosides in combination with penicillin has been proposed but the benefit of this combination has never been proven.[9] We therefore performed a retrospective multicentre review of the clinical features of GBS PJI, surgical management, and type and duration of antibiotic therapy. We compared the surgery undertaken with that recommended in a published

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algorithm for management of PJI, and evaluated the outcome of GBS PJI episodes and factors associated with treatment failure.[9]

Methods

Diagnosis of GBS PJI

Only adult patients (aged >18 years) were reviewed. Identification of GBS in synovial fluid or periprosthetic tissue by either culture or by eubacterial polymerase chain reaction (16-S-rRNA), plus at least one of the following criteria were required: sinus tract, pus surrounding the prosthesis, or inflammation in tissue on histological examination (≥10 neutrophils/high power field). In cases of polymicrobial infection involving bacterial skin flora such as coagulase-negative staphylococci and *Propionibacterium* spp., at least two positive culture results were required. Serotyping of GBS was not performed. Patients were not investigated for GBS colonisation.

Definition and data collection of GBS PJI episodes

An episode included the period from diagnosis of GBS PJI to the end of antimicrobial treatment. All surgical procedures within this time interval were assigned to the same episode. A relapse was defined as recurrence of PJI ≤2 weeks after completion of antimicrobial therapy, irrespective of microbiological results, or recurrence of PJI >2 weeks after completion of antimicrobial therapy with evidence of GBS. The two-week limit in this definition is based on the reduced sensitivity of culture in PJI observed after antimicrobial therapy.[10] A reinfection was defined as recurrence of PJI with another pathogen >2 weeks after completion of antimicrobial therapy.

Episodes were collected from four Swedish and six Swiss centres in a review of their local database of PJIs and/or microbiological data bank for GBS. These databases were based on local institutional policies and established from 1990 to 2005. Data were collected until 30 March 2008. For each episode, the patient's records were reviewed by a local investigator and data recorded anonymously on a questionnaire with 23 clinical, microbiological, radiological, therapeutic and patient-specific variables. The questionnaire was first validated in one centre (Liestal, Switzerland), which later performed the data analysis. The following variables were included for outcome analysis: age, sex, diabetes, obesity, chronic skin disease, number of comorbidities, and American Society of Anesthesiology (ASA) score. This is a global score that assesses the physical status of patients before surgery: ASA 1 corresponds to a normal healthy patient, ASA 2 to a patient with mild systemic disease, and ASA 3 to a patient with severe systemic disease.

Evaluation of surgical and medical treatment

GBS PJI episodes were analysed in two groups. Group 1 included only episodes in which retention of the implant was initially attempted, irrespective of subsequent surgery within the same episode. Group 2 included all episodes, but only the final surgical intervention of each episode was considered for outcome analysis. Hence, episodes of group 1 were also part of group 2 (Figure 1). Surgical intervention for each GBS PJI episode was evaluated with reference to a previously published algorithm.[9] This algorithm recommends exchange of the implant if symptoms have lasted >3 weeks, the prosthesis is unstable, or a difficult-to treat micro-organism is involved (the last applying in this study in which there was polymicrobial infection with GBS and, for example, rifampin-resistant staphylococci or fungi).[10] A two-stage exchange is recommended if tissue damage is moderate or severe, or if a difficult-to-treat micro-organism is present. Moderate tissue damage includes small wounds without discharge, and severe includes wound discharge, sinus tract, and abscess. Removal of the prosthesis without reimplantation is recommended if exchange of the implant offers no functional improvement (e.g. confinement to bed, paraplegia). Applied to GBS PJI, the algorithm recommends debridement and retention of the implant only if the duration of symptoms is ≤3 weeks, the implant is stable and the soft tissue is intact or only slightly damaged. The variables for the evaluation of medical treatment included treatment duration, antimicrobial compound, and use of rifampin and/or aminoglycosides.

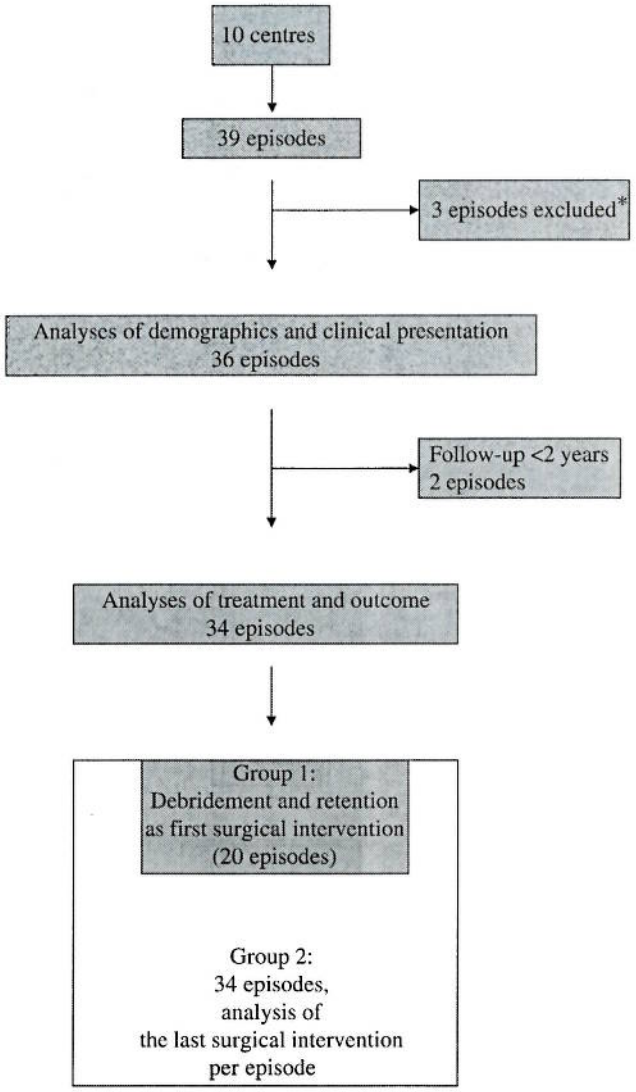

Figure 1. Flow chart of the study. *Two patients declined informed consent and one patient with a psychiatric disorder performed repetitive self-inoculation of the prosthetic joint.

Follow-up examinations

All episodes had follow-up investigations, either within a cohort in specialised centres, or as part of this study. Patients belonging to the latter group were contacted and invited to one of the participating centres for clinical, laboratory, and radiological examination in accordance with a predefined protocol. Event-free episodes with a follow-up of <2 years were excluded from treatment and outcome analysis (Figure 1), because treatment method is associated with outcome, and final outcome should not be evaluated prior to 2 years.[11]

Outcome analyses

In group 1 (initial debridement and retention of the implant), removal of the implant within the same episode was the end point and defined as failure. In group 2 (all GBS PJI episodes, considering only the final surgical intervention per episode), two end points were included in the outcome analysis for failure: (a) relapse and (b) permanent removal of the implant. The latter end point was included in the analyses because cure of PJI must consist of both eradication of the micro-organism and retention of functional mobility.

Patient consent and ethical approval

Written patient consent was obtained from all individuals. The study was approved by the ethical committees of the corresponding centres in Switzerland and Sweden.

Statistical analysis

Univariate assessment of selected risk factors by χ^2-test, Fisher's exact test, and Student's *t*-test where appropriate were performed, as well as multivariate analyses with a logistic regression model. Variables with two-tailed $P < 0.05$ were considered significant. The statistical software used was S-Plus 2000.

Results

Frequency and demographics

Thirty-nine episodes of GBS PJI were identified in the 10 institutions. The median frequency of GBS hip or knee PJI per centre was 0.5 per year [interquartile range (IQR): 0.43–0.65 per year]. The frequency of GBS PJI in comparison to all PJI per centre was 3% (median; IQR: 3.0–4.2%). Three episodes were excluded (Figure 1). Hence, 36 episodes of GBS PJI in 34 patients (34 episodes plus two relapses) were included for analysis, relating to 23 hip and 13 knee prostheses. The median age was 71 (IQR: 65–79) years; the sexes were equally represented.

Clinical presentation and comorbidity

The interval from implantation of the prosthesis to onset of symptoms ranged from two weeks to 25 years. However, 75% of episodes occurred between 3 and 24 months after implantation [classified as delayed infection: 16 (44%)] or occurred ≥24 months after implantation [late infection: 11 (31%)].[10] Signs and symptoms are shown in Table I. Damaged soft tissue and pain were present in 89% and 83%, respectively, of the episodes. In 25 (69%) episodes, PJI presented with acute symptoms and the diagnosis was established within a few days (median: 3; IQR: 1–5 days). In the remaining 11 (31%) episodes, the patient's history indicated that symptoms were acute, but the diagnosis was not established early. In these episodes, a doctor's visit was delayed until a sinus tract was evident in six episodes, and symptoms were possibly misinterpreted in a further five episodes (for example as infection of unknown origin or joint pain due to obesity). Only three of the 34 (9%) patients did not have any comorbidity. Fifteen (44%) patients had ≥3 comorbidities. The most frequent diseases are listed in Table II. In 27 (79%) patients, the ASA score was ≥2. None of the selected variables (see methods) was associated with poor outcome.

Microbiology

GBS was identified by standard culture in 35 episodes and by 16-S-rRNA in one episode. In 11 (31%) episodes, GBS was part of a polymicrobial infection, including coagulase-negative staphylococci (six episodes), *Staphylococcus aureus* (three episodes), *Pseudomonas aeruginosa* (one episode) and *Ureaplasma urealyticum* (one episode). In three (8%) episodes, GBS also grew in blood cultures. Antimicrobial susceptibility testing results for clindamycin and erythromycin was available in 32 of 36 episodes, revealing that two (6%) strains were resistant to both compounds.

Table I
Signs and symptoms of 36 episodes with group B streptococcus hip or knee periprosthetic joint infection

Signs and symptoms	No. of episodes
Compromised soft tissue	32 (89%)
Slightly damaged soft tissue[a]	13 (36%)
Moderately damaged soft tissue[b]	8 (22%)
Severely damaged soft tissue[c]	11 (31%)
Pain	30 (83%)
Fever	18 (50%)
Chills	10 (28%)
Bacteraemia	3 (8%)
Loose implant	10 (28%)

[a] Slightly damaged soft tissue included erythema and induration.
[b] Moderately damaged soft tissue included small wounds without discharge.
[c] Severely damaged soft tissue included wound discharge, sinus tract, and abscess.

Treatment and outcome

These analyses included 34 episodes. Two were excluded because follow-up was <2 years (Figure 1), but no infection-related event was recorded at 1-year follow-up. In 20 of 34 episodes, debridement was the initial surgical treatment (group 1); in five of these the implant was ultimately removed (Table III). The final surgical interventions in group 2 (all GBS PJI episodes, Table IV) included debridement with retention in 15 (44%) episodes, one-stage exchange in three (9%), two-stage exchange in 12 (35%), and removal of the implant in four (12%).

Intravenous antibiotic treatment included penicillin derivatives in 21 (62%) episodes, cephalosporins in nine (26%), vancomycin in two (6%), and clindamycin in two (6%). In seven (21%) episodes, treatment was combined with an aminoglycoside. The most common oral antibiotics were penicillin derivatives in 15 (44%) episodes and clindamycin in eight (24%); others included cefuroxime, levofloxacin, flucloxacillin, and linezolid. In 13 (38%) episodes, rifampin was part of combination therapy, although in six of these, rifampin-susceptible staphylococci were also involved. The median duration of intravenous treatment was 24.5 (IQR: 12–43) days. Total treatment duration was 3.2 (2.3–4.5) months for hip PJI and 3.3 (1.6–6.0) months for knee PJI.

In group 1 (initial debridement with retention of the implant), the failure rate was 35%. Ten of 20 episodes fulfilled the criteria set out in the algorithm (Table III) and none of these had treatment

Table II
Common comorbidities of 34 patients (36 episodes) with group B streptococcus hip or knee periprosthetic joint infection

Comorbidity	No. of patients
Ischaemic heart disease	10 (29%)
Chronic skin disease[a]	9 (26%)
Arterial hypertension	8 (24%)
Obesity (BMI ≥30 kg/m^2)	8 (24%)
History of or active cancer	5 (15%)
Diabetes	5 (15%)
Immunosuppressive therapy	4 (12%)
Renal insufficiency (GFR <30 mL/min)	4 (12%)
History of stroke	4 (12%)

BMI, body mass index; GFR, glomerular filtration rate.
[a] Including skin ulcers, dermatitis irrespective of origin, and psoriasis.

Table III
Characteristics of 20 episodes with initial debridement and retention of the prosthesis (group 1 analyses)

No.	Joint	Time from onset of symptoms until diagnosis (days)	Time from onset of symptoms until debridement (days)	Implant	Soft-tissue damage	Type of surgery	No. of revisions	Compliant with published algorithm[a]	Final surgery[b]	Interval[c] (days)	Duration of antibiotics (weeks)	Outcome of debridement	Follow-up
1	Knee	7	10	Stable	Slight	Open	1	Yes	–	–	26	Cure	4.3 years
2	Hip	5	5	Stable	Slight	Open	1	Yes	–	–	12	Cure	2.0 years
3	Hip	5	5	Stable	Intact	Open	1	Yes	–	–	21	Cure	5.7 years
4	Hip	2	17	Stable	Slight	Open	1	Yes	–	–	26	Cure	2.0 years
5[d]	Knee	6	8	Stable	Slight	Open	1	Yes	–	–	246[d]	Cure	6.1 years
6	Knee	6	6	Stable	Slight	Open	1	Yes	–	–	7	Cure	2.5 years
7	Knee	5	5	Stable	Slight	Arthroscopic	3	Yes	–	–	14	Cure	6.1 years
8	Knee	3	3	Stable	Slight	Open	2	Yes	–	–	26	Cure	2.0 years
9[e]	Hip	1	2	Stable	Not classified[e]	Open	3	Yes[e]	–	–	8	Cure	2.5 years
10	Knee	1	2	Stable	Slight	Open	1	Yes	–	–	29	Cure	2.0 years
11	Hip	12	40	Stable	Moderate	Open	1	No	–	–	13	Cure	2.1 years
12	Knee	1	3	Stable	Moderate	Open	1	No	–	–	26	Cure	2.3 years
13	Hip	59	61	Stable	Moderate	Open	1	No	–	–	12	Cure	2.2 years
14	Hip	61	68	Stable	Slight	Wound revision	1	No	–	–	12	Failure	4.2 months
15[f]	Hip	1[f]	1	Stable	Severe[f]	Open	5	No	2-St-E	16	38	Failure	–
16	Hip	29	34	Loose	Severe	Open	2	No	–	–	12	Failure	5.0 months
17	Hip	8	9	Stable	Severe	Open	1	No	2-St-E	24	38	Failure	–
18[g]	Knee	Unknown[g]	1	Stable	Severe	Open	1/12[g]	No	Removal of implant	14	27	Failure	–
19	Hip	33	34	Loose	Intact	Arthroscopic	2	No	1-St-E	84	18	Failure	–
20	Knee	5	6	Stable	Severe	Arthroscopic	3	No	2-St-E	41	15	Failure	–

1-St-E, one-stage exchange; 2-St-E, two-stage exchange.

[a] Criteria for debridement and retention of the implant were compared with previously published recommendations.[9]

[b] The final surgery was assigned to the episode, if failure of debridement and retention occurred while antimicrobial treatment was ongoing.

[c] The interval included the period from the last debridement until final surgical intervention.

[d] Episode 5. Because the patient was confined to bed and further (potential) surgeries were to be avoided, she was treated with oral antibiotics after debridement for 4.7 years. However, 2 years after stopping suppressive treatment, no signs of relapse were evident on follow-up examinations.

[e] Episode 9. Lack of wound healing was noticed shortly after surgery. Soft tissue damage could not be classified according to the defined criteria, since they commonly refer to damage after initial wound healing. Because of rapid intervention within the same hospitalisation as for prosthesis implantation, open debridement and retention of the implant was interpreted as a surgical procedure in accordance with the algorithm.

[f] Episode 15. The patient was treated with methotrexate for rheumatoid arthritis and claimed no symptoms until 1 day before clinical presentation. Intraoperative findings revealed severely damaged periprosthetic soft tissue.

[g] Episode 18. Duration of symptoms is unknown. Diagnosis was established at hospitalisation. After debridement, drainage was inserted into the joint and daily lavage performed for 12 days.

Table IV
Outcome of 34 episodes with group B streptococcus (GBS) hip or knee periprosthetic joint infection after final surgical intervention (group 2 analyses)

Outcome	No.	Cure from GBS	Relapse	Reinfection
Debridement with retention	15	13[a]	2	0
One-stage exchange	3[b]	3	0	0
Two-stage exchange	12[b]	12	0	2[c]
Removal of the implant	4[b]	4	0	2[d]

[a] One patient (confined to bed) was treated with oral antibiotics after debridement for 4.7 years because potential further surgery (although in retrospect not necessary) was declined. However, 2 years after stopping treatment, there were no signs of relapse on follow-up examinations.

[b] Five episodes were initially treated with debridement and retention (see also Table III), but the final surgical intervention for the corresponding episode included one-stage exchange in one episode, two-stage exchange in three episodes, and permanent removal of the implant in one episode.

[c] At 6 weeks and 1.2 years after stopping correct antimicrobial treatment, reinfection of the prosthesis occurred with *Staphylococcus epidermidis* and *S. aureus*, respectively.

[d] At 9.5 months and 3.4 years after stopping correct antimicrobial treatment, an infection occurred in the area of the Girdlestone pocket with *S. epidermidis* and GBS, respectively.

failure. By contrast, 7 of 10 patients who did not fulfil the criteria failed ($P = 0.003$). The criteria for implant retention that were not fulfilled were mainly prolonged duration of symptoms and extent of soft tissue damage. In two of the seven episodes with failure, relapse with evidence of GBS occurred 4.2 and 5 months after stopping antibiotics. In the other five, failures were postulated while antimicrobial treatment was ongoing (Table III) for reasons that included impaired wound healing, persistent pain, and implant loosening. In these five episodes, the subsequent surgery was allocated to the same GBS PJI episode for further analysis in group 2.

In group 2 (all GBS PJI episodes), the final surgical intervention was in accord with the algorithm in 26 (76.5%) of 34 episodes.[9] In the other eight episodes, reasons for conflict between surgical intervention and the algorithm included prolonged duration of symptoms or extent of soft-tissue damage in cases of debridement with retention or one-stage exchange. In one of these eight episodes, retrospective analysis suggested that a two-stage exchange was planned, but permanent removal of the implant was performed. Surgery according to the algorithm was associated with a successful outcome when relapse alone was considered as failure ($P = 0.049$), but this association failed to reach statistical significance when both relapse and permanent removal of the implant were considered as treatment failure (multivariate analysis, odds ratio 2.77, 95% confidence interval: 0.91–8.36). Treatment duration of <12 weeks (six episodes, ranging from 5 to 11 weeks) was not associated with treatment failure. Also, lack of aminoglycoside combination therapy (27 of 34 episodes) was not associated with treatment failure, irrespective of treatment duration and surgical intervention. Similarly, lack of rifampin combination therapy (21 of 34 episodes) was not associated with treatment failure either for monomicrobial GBS infections or for all episodes, irrespective of treatment duration and surgical intervention. Twenty-eight (82%) GBS PJI episodes had an infection-free follow-up of ≥2 years (median: 2.8; IQR: 2.1–4.7 years) and were classified as cured. The remaining six episodes consisted of two (6%) relapses with evidence of GBS and four reinfections with other organisms (Table IV).

Discussion

The incidence of invasive GBS infections in non-pregnant adults is increasing.[2] It is conceivable that the frequency of GBS PJI will also increase. The median frequency of GBS PJI at the participating centres was 3% in this study and similar to that of other case series.[7,8,13] A search in the MEDLINE database from 1977 to 2009 revealed 75 episodes of GBS PJI with different levels of information.[3–8,12–22]

The median age in our study was 71 years, similar to that of other reports, and no different from that of patients with PJI caused by other pathogens.[3–8,11–22] The vast majority of patients in our study and in other studies had one or more chronic underlying diseases.[3,6,7,14] In our study, 75% of the episodes were diagnosed ≥3 months after implantation, and at least 69% presented with acute symptoms, indicating that GBS PJI occurs predominantly by haematogenous seeding. Similarly, from 65 published GBS PJI episodes with sufficient information, 51 (78%) occurred ≥3 months after implantation and 57 (88%) presented with acute symptoms.[3–8,12,14–22] In 31% of our episodes, GBS was part of a polymicrobial infection, and staphylococci were the most frequently isolated co-micro-organism. In these episodes, the mode of infection in prosthetic joints is difficult to determine. The optimal treatment strategy for GBS PJI is unknown. A recent study that compared GBS PJI with those due to other pathogens found GBS infection to be an independent risk factor for treatment failure.[23]

We first investigated the GBS PJI episodes in which debridement and retention of the implant was initially attempted. This surgical procedure is less invasive and has a lower complication rate than a prosthesis exchange. Consequently, the patient population that is typically affected by GBS disease, namely, the elderly with several comorbidities, will likely benefit the most from this treatment option. Our study supports the view that debridement and implant retention in GBS PJI is safe, provided that the duration of symptoms is short, the implant is stable, and the soft tissue damage is minor. Not fulfilling these criteria was significantly associated with implant removal. Hence, rapid access to surgical intervention must be guaranteed for patients with a PJI, because the delay of treatment may exacerbate soft tissue damage, which increases the risk of failure of debridement and implant retention.[24]

The final outcome of our GBS PJI episodes was good, irrespective of study centre. In 94% (32 of 34) of the episodes, the GBS infection was cured; in 82% (28 of 34), the infection-free follow-up was ≥2 years; and in 82% (28 of 34), functional mobility of the joint was maintained. Our finding that most GBS PJI episodes occur in patients with several comorbidities and a high ASA score are consistent with other published reports. These variables, rather than GBS itself, could act as risk factors for complications such as reinfection or treatment-related death.[25,26]

Penicillin is the antimicrobial agent of choice for GBS infection. The recommendation to co-administer an aminoglycoside for 2–4 weeks is partially based on *in vitro* results that implied an increased killing effect.[9,27] However, recent investigations of clinical GBS isolates could not confirm the superiority of this combination versus penicillin alone.[28] Also, in a GBS endocarditis study, a β-lactam–aminoglycoside combination did not show any advantage over β-lactam monotherapy for duration of hospitalisation or mortality.[29] Cunningham *et al.*[19] described a case of relapsing GBS PJI with a penicillin-tolerant strain in which such combination therapy resolved the symptoms. In that case, no surgical intervention was performed in the first episode, and penicillin tolerance was investigated after relapse occurred. The occurrence of penicillin tolerance in clinical GBS isolates, irrespective of site of infection, varies among different studies, ranging from 5% to 15%.[30] However, the influence of tolerance on the outcome of GBS PJI is unknown. We did not look for penicillin tolerance in any of our GBS isolates. Neither our nor published data allow a firm conclusion about aminoglycosides as adjunctive therapy.[5,6,19] The lack of clinical evidence showing a benefit with the combination therapy together with the evidence of aminoglycoside nephrotoxicity, and the vulnerability associated with advanced age and comorbidities

commonly found in patients with GBS PJI support a cautious approach to aminoglycoside use.

Our study has a number of limitations. The absolute number of GBS PJI is small, which limits the interpretation of the statistical results. However, the inclusion criteria were strict: only GBS PJI episodes with a follow-up examination of ≥2 years were selected. Another limitation is the partially retrospective design, which may allow case selection and categorisation bias. Because of the low incidence of PJI, most studies are often feasible only in retrospect.[31] Moreover, in 32 (94%) of the 34 GBS PJI episodes, the potential for bias was counterbalanced by the fact that the final outcome was not known at the time of their entry into a PJI cohort (16 episodes in three centres) or into the study (16 episodes in seven centres). The latter group was also prospectively followed and invited for a final follow-up examination. Finally, the grading of soft tissue damage was assessed in retrospect, which may have led to categorisation bias of an important variable, although the definitions of soft tissue damage were detailed and the case questionnaire was previously validated.

Several conclusions can be drawn from our study and previous reports. First, GBS PJI commonly occurs in patients with several comorbidities and often presents with acute symptoms and damaged periprosthetic soft tissue. Second, infection frequently presents ≥3 months after implantation, indicating a predominantly haematogenous route. Third, debridement with retention of the implant can be successfully performed if the duration of symptoms is short, the implant stable, and the tissue damage minor.

Conflict of interest statement
None to declare.

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Appendix

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