Artificial Organs

Therapy and Outcome of *Staphylococcus aureus* Infections of Intracorporeal Ventricular Assist Devices

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Abstract: Infection of the driveline or pump pocket is a common complication in patients with ventricular assist devices (VADs) and *Staphylococcus aureus* is the main pathogen causing such infections. Limited evidence is currently available to guide the choice of antibiotic therapy and the duration of treatment in these patients. Patients at the University Medical Center Utrecht who developed a VAD-related *S. aureus* infection between 2007 and 2016 were retrospectively assessed. Blood culture isolates were typed by whole genome sequencing to differentiate between relapses and reinfections, and to determine whether antibiotic therapy had led to acquisition of resistance mutations. Twenty-eight patients had *S. aureus* VAD infections. Ten of these patients also suffered *S. aureus* bacteremia. Discontinuation of antibiotic therapy was followed by relapse in 50% of the patients without prior *S. aureus* bacteremia and in 80% of patients with bacteremia. Oral cephalexin could ultimately suppress the infection for the duration of follow-up in 8/8 patients without *S. aureus* bacteremia and in 3/6 patients with *S. aureus* bacteremia. Clindamycin failed as suppressive therapy in 4/4 patients. Cephalexin appears an adequate choice for antibiotic suppression of VAD infections with methicillin-susceptible *S. aureus*. In patients without systemic symptoms, it may be justified to attempt to stop therapy after treatment of the acute infection, but antibiotic suppression until heart transplant seems indicated in patients with *S. aureus* bacteremia. **Key Words:** *Staphylococcus aureus*—Bacteremia—Ventricular assist device infection—Cephalexin—Suppression therapy.

Intracorporeal ventricular assist devices (VADs) are powered by an external battery through a driveline, which penetrates the skin and constitutes an open connection from the outside world to the pumps and the pockets, rendering the VAD systems prone to bacterial colonization and subsequent infection. Recent cohort studies report infection rates of 22–40%, depending to a large degree on the duration of mechanical circulatory support (MCS) (1–4). These infections may present with symptoms at the driveline tunnel or at the pump pocket, they may cause fistulae and abscesses, and may lead to systemic symptoms, bloodstream infection, sepsis, and death. The most common pathogen is *Staphylococcus aureus*; other frequently encountered bacteria include coagulase-negative staphylococci, enterococci, *Enterobacteriaceae*, nonfermentative Gram-negatives, and *Candida* species (3,5–8).

Over the last years, several reports have been published describing incidence, risk factors and general management of VAD infections (1–3), but details of antibiotic policies have thus far mostly been described in case reports and small case series (5,8–10). This study, therefore, retrospectively assessed the antibiotic treatment and the outcome of VAD-infections caused by *S. aureus*, the most frequent and the most virulent pathogen in our population.

doi: 10.1111/aor.13159

Received February 2018; revised March 2018; accepted March 2018.

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PATIENTS AND METHODS

Inclusion and data

Patients with intracorporeal VADs implanted at the University Medical Center Utrecht (UMCU) were included if they had culture-proven infections of the VAD driveline or pump system with *S. aureus* between January 1st, 2007 and March 31st, 2016. Patient follow-up was recorded until October 1st, 2016. Post-study follow-up of this group revealed one relapse of bacteremia two months later, and it was decided to include this event in the analysis. VAD patients with infections were retrieved from the VAD complication registry of the Department of Cardiothoracic Surgery. Clinical data and patient data were obtained from the patient records and the antibiotic stewardship consultation system. A waiver was obtained for institutional review board approval.

Definitions and analysis

S. aureus VAD infection was defined as: (i) signs of infection around the pump system or driveline (purulence, redness, tenderness, swelling, and/or abscesses) and (ii) a positive culture of the pump system, pocket, driveline or exit site with *S. aureus*. In practice, all patients with *S. aureus* cultured from these sites had such symptoms and were diagnosed with VAD infection. *S. aureus* bacteremic VAD infection was defined as a combination of (i) *S. aureus* bacteremia, (ii) a positive culture of the pump system, pocket or driveline exit site with *S. aureus*, and (iii) identical susceptibility patterns of these isolates. "Continued suppression therapy" was defined as continued oral antibiotic therapy after an infectious episode, targeting *S. aureus* and continued until death, heart transplant, end of the study, or until failure, that is, breakthrough of *S. aureus* infection requiring a switch in antibiotic therapy. If antibiotics were switched due to toxicity (mostly rash or nausea), this was still considered a single episode. Relapse was defined as infection with *S. aureus* after discontinuation of antibiotic therapy, requiring antibiotic treatment.

Extracted data were used to construct timelines depicting infections, culture results, major medical events, and antibiotic usage. Every time a patient suffered an *S. aureus* infection, either a first infection, a breakthrough infection or a relapse, this was included as a new episode and the therapy and outcome of this treatment was assessed. Outcomes could be: (i) in follow-up without *S. aureus* complications, (ii) heart transplant without intercurrent infectious complications due to *S. aureus*, (iii) death without intercurrent infectious complications due to *S. aureus*, (iv) breakthrough-infection with *S. aureus*, or (v) relapse of *S. aureus* infection. Patients with and without demonstrated *S. aureus* bacteremia were evaluated separately. Patients who developed localized infection first and bacteremia at a later stage were analyzed within the "no bacteremia"-group first and subsequently in the bacteremia group.

Whole-genome sequencing (WGS) and comparative genome analysis

WGS was performed on the *S. aureus* blood isolates and five available local isolates. In case of relapsing infection, isolates from the different episodes were sequenced. Isolates were cultured overnight at 37°C on blood agar plates. Subsequently one colony was transferred to Lysogeny Broth and incubated overnight at 37°C. From this culture DNA was isolated using the QIAcube DNeasy Blood & Tissue kit (Qiagen, Venlo, The Netherlands). Library preparation used the Illumina Nextera XT DNA Sample Preparation kit. Sequencing was performed on an Illumina NextSeq with the mid-output 2× 150 bp kit or an Illumina MiSeq V(2) kit with a 2 × 250 bp output using paired-end sequencing approach (Illumina, San Diego, CA, USA).

Sequence reads were first quality-filtered using seqtk with option "trimfq -q 0.01" (version 1.2-r94, https://github.com/lh3/seqtk) and then assembled using SPAdes assembler (version 3.6.2) using the "–only-assembler –careful" option (11). SeqSphere+ (version 4.0.2; Ridom GmbH, Münster, Germany) was used to build a core genome multi-locus sequence typing (cgMLST) scheme, based on the genes present in 115 *S. aureus* strains downloaded from the NCBI Genbank database (Supporting Information Table). The cgMLST scheme containing 1580 core genes was used to identify allele differences in core genes of the newly sequenced strains. Based on previous unpublished data isolates with less than 25 alleles difference were considered as indistinguishable. A cgMLST-based phylogenetic tree was constructed to visualize the relatedness between the isolates from different infectious episodes and from different patients.

To identify antibiotic resistance genes (ARGs), genomes of the sequenced isolates were first annotated using Prokka (version 1.11) using its "–usegenus" option (12) Next, protein sequences from these genomes were aligned to the ResFinder (version 2.1; downloaded on June 30, 2017 from its BitBucket repository at https://bitbucket.org/

genomicepidemiology/resfinder_db) database using Blast+ (version 2.2.29) (13). Finally, presence of an ARG was based on the minimum alignment length of at least 90% and minimum alignment length of 60%, which are default parameters of the ResFinder tool.

RESULTS

Patients

At the start of the study 10 patients at the UMCU had an intracorporeal VAD in situ; during the inclusion period, 197 patients had an intracorporeal VAD implanted. Forty-five VAD-patients died, 71 patients received a heart transplant, and in 7 patients the VAD was removed without need for further MCS. During this period, 61 patients sustained one or more episodes of VAD-related infections: 37 patients suffered at least one episode of bacteremia, 22 of which had positive cultures of the exit site, driveline or pump pocket infections. An additional 24 patients had localized infections of the pocket or driveline (i.e., compliant with the two criteria for VAD-infection) without demonstrated bacteremia.

Twenty-eight patients had *S. aureus* VAD infections with positive cultures of the exit site, driveline or pump pocket, and were included in this study. In addition, three VAD patients suffered *S. aureus* bacteremia without signs of localized infection (and were therefore not included in this study). Basic patient characteristics and outcome are shown in Table 1. Seven patients died during the study; cause or contributing factor in their deaths were thrombosis of the LVAD (2 patients), pump failure (3 patients), intracerebral hemorrhage (3 patients), complications of sepsis (3 patients), and failure of the right ventricle (1 patient). Death could in some cases be attributed to a combination of pathologies. All patients who received a heart transplant, survived until the end of the follow-up period of this study and none suffered postoperative infections by *S. aureus*. Peri-operative antimicrobial prophylaxis at time or heart transplant consisted of vancomycin plus cefuroxime for a duration of 48 h in patients with VAD therapy. In some patients in this cohort, surgery was performed to drain abscesses or remove fistulae. In some patients the VAD was removed due to (temporary) recovery of the heart function or exchanged because of malfunction (thrombosis or damage to the driveline); infection by itself did not lead to VAD removal or exchange.

In total, 10 patients (numbered SAB 1–10 for "*Staphylococcus aureus* Bacteremia," Fig. 1) developed bacteremia with *S. aureus* at some stage, six of which suffered bacteremia at the first presentation of *S. aureus* infection; all had concurrent driveline or pocket infections identified as focus of the bacteremia. Twenty-two patients presented with a *S. aureus* infection of the driveline or pump but without bacteremia, four of which (18%) developed *S. aureus* bacteremia at a later stage. The 18 patients who did not develop *S. aureus* bacteremia were numbered BCN 1–18 for "Blood Culture Negative" (Supporting Information Figure).

TABLE 1. Patient and device characteristics of patients with *Staphylococcus aureus* ventricular assist device infections

Risk factor	Patients with VAD infections ($N = 28$)
Age at time of VAD implant, median	47 years (range 17–69 years)
Female gender	7 (25%)
Left Ventricular Assist Device (LVAD)	28 (100%)
VAD type	Heartmate II: 22 (79%) Heartware: 5 (18%) Heartmate III: 1 (4%)
Time from implant of VAD to first culture positive with *S. aureus,* median	40 weeks (range 3–172 weeks)
Time from implant of VAD to first positive blood culture with *S. aureus* (n=10), median	23 weeks (range 7–170 weeks)
Total duration of MCS during the study period, mean	140 weeks (range: 39–298 weeks)
Outcome at end of study period	Heart transplant: 10 (36%) In follow-up: 11 (39%) Death: 7 (25%)

LVAD, left ventricular assist device; MCS, mechanical circulatory support; VAD, ventricular assist device.

Susceptibility of the *S. aureus* strains

All isolated *S. aureus* strains were susceptible to methicillin, vancomycin, linezolid, tetracycline, rifampicin, and linezolid. Four of the 28 patients (14%) had or developed strains resistant to cotrimoxazole, and three (11%) to ciprofloxacin. Two patients (7%) had strains resistant to erythromycin and one to clindamycin (4%). Furthermore, in the strain from patient SAB1 erythromycin and clindamycin resistance developed under clindamycin treatment (the isolate in week 178).

Therapy in patients without (or prior to development of) bacteremia

Twenty-two patients experienced a total of 38 episodes of VAD infections without bacteremia. In 24 episodes, the antibiotic therapy was discontinued after a minimum treatment duration of 2 weeks, leading to 14 relapses (two with bacteremia) and

two recurrences of fistulae, that is, a failure rate of 67% (16/24). In eight patients, no relapse was recorded during a median follow-up of 169 days (range 22–908): three patients were still in follow-up at the end of this study, three had received a heart transplant and two died from unrelated causes.

After 14 infectious episodes, oral suppression therapy was continued indefinitely: four patients experienced breakthrough infections and one had a septic episode due to obstruction of a permanent fistula, that is, a failure rate of 36% (5/14) (Fig. 2). Five patients continued their antibiotic suppression therapy until heart transplant, one until death from

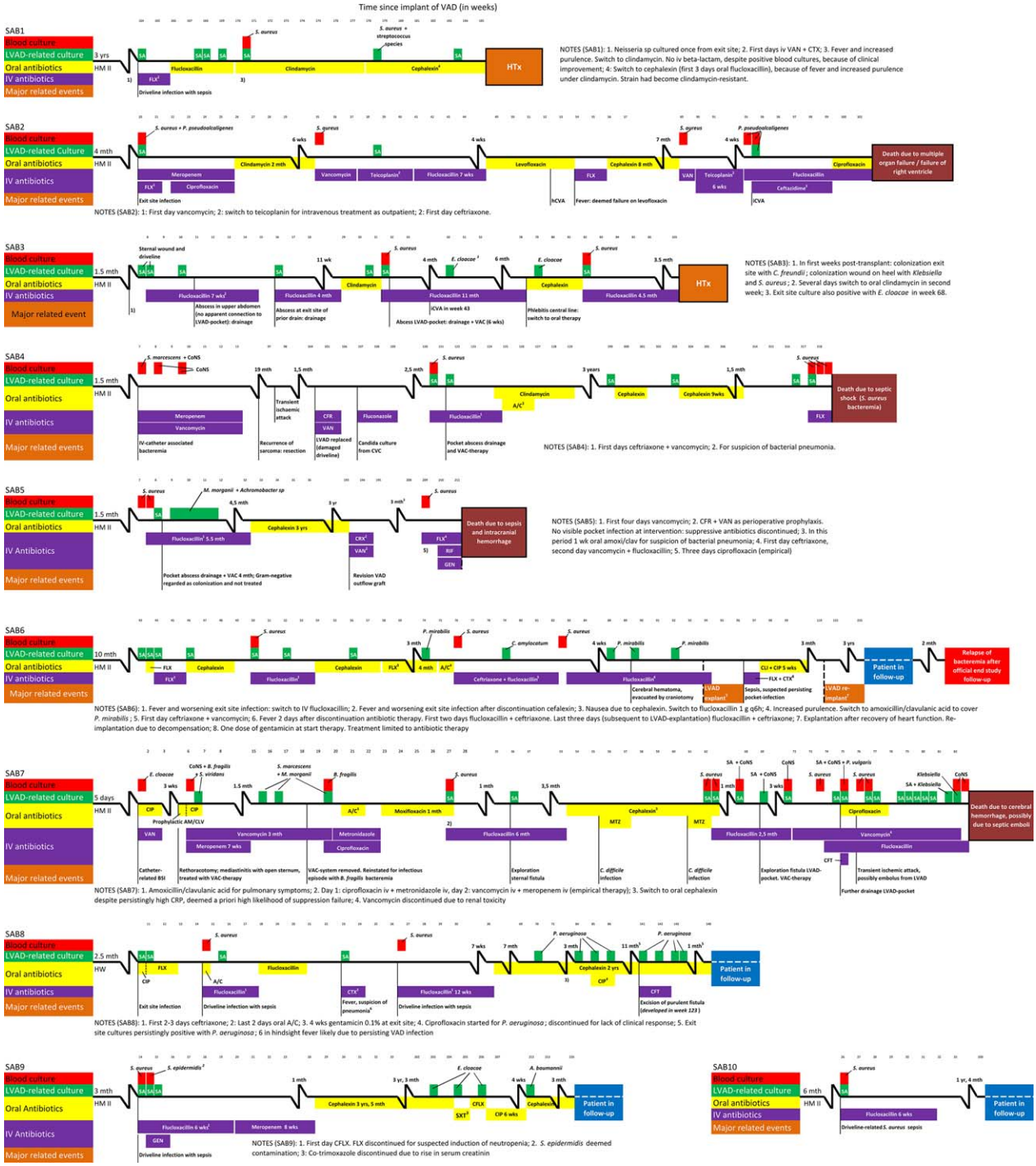

FIG. 1. Timelines of patients with *Staphylococcus aureus* ventricular assist device (VAD) infections with *S. aureus* bacteremia. Numbers above timelines indicate weeks since implant of intracorporeal VAD. LVAD-related culture: culture from driveline tunnel, driveline tunnel, pump pocket (abscess) or fistula with connection to pump pocket. VAD patients with blood cultures positive for *S. aureus* are numbered SAB1-SAB10. Time (in days, months, or years) at beginning of timeline indicates the interval between VAD implantation and the first episode of VAD infection or bacteremia, also if caused by micro-organisms other than *S. aureus*. The abbreviation below the start of the timeline indicates the type of VAD. Abbreviations: A/C = amoxicillin/clavulanic acid; BSI = Bloodstream Infection; CFLX = cephalexin; CFR = cefuroxime; CIP = ciprofloxacin; CLI = clindamycin; CFT = ceftazidime; CTX = ceftriaxone; CVC = central venous catheter; FLX = flucloxacillin; GP = general practitioner; hCVA = hemorrhagic cerebrovascular accident; HM II = Heartmate II ventricular assist device; HM III = Heartmate III ventricular assist device; HTx = Heart Transplant; HW = Heartware ventricular assist device; iCVA = ischemic cerebrovascular accident; LVAD = Left ventricular assist device; MTZ = metronidazole; PIP/TZ = piperacillin-tazobactam; RIF = rifampicin; SA = Staphylococcus aureus (in LVAD-related tissue culture or pus culture); TRM = trimethoprim; VAC = Vacuum Assisted Closure; VAN = vancomycin; VOR = voriconazole. Micro-organisms: *A. baumannii* = *Acinetobacter baumannii; C. jeikeium* = *Corynebacterium jeikeium; C. koseri* = *Citrobacter koseri;* CoNS = coagulase-negative staphylococci; *E. cloacae* = *Enterobacter cloacae; E. faecalis* = *Enterococcus faecalis; E. faecium* = *Enterococcus faecium; K. oxytoca* = *Klebsiella oxytoca; M. morganii* = *Morganella morganii; P. aeruginosa* = *Pseudomonas aeruginosa; P. alcaligenes* = *Pseudomonas alcaligenes; S. apiospermum* = *Scedosporium apiospermum; S. aureus* = *Staphylococcus aureus; S. epidermidis* = *Staphylococcus epidermidis; S. maltophilia* = *Stenotrophomonas maltophilia; S. marcescens* = *Serratia marcescens*. [Colour figure can be viewed at wileyonlinelibrary.com]

unrelated causes, and three until the end of the follow-up period.

Therapy in patients with *S. aureus* bacteremia

Ten patients (SAB1-SAB10) experienced a total of 23 episodes of *S.aureus* bacteremia or of relapse of VAD infection with systemic symptoms after bacteremia. In four episodes intravenous antibiotic therapy was continued until death. In one episode, intravenous therapy was continued until heart transplantation. In eight episodes, the antibiotic therapy was stopped after a minimum of 6 weeks treatment, with a relapse rate of 89% (7/8); two of these relapses were complicated by severe sepsis

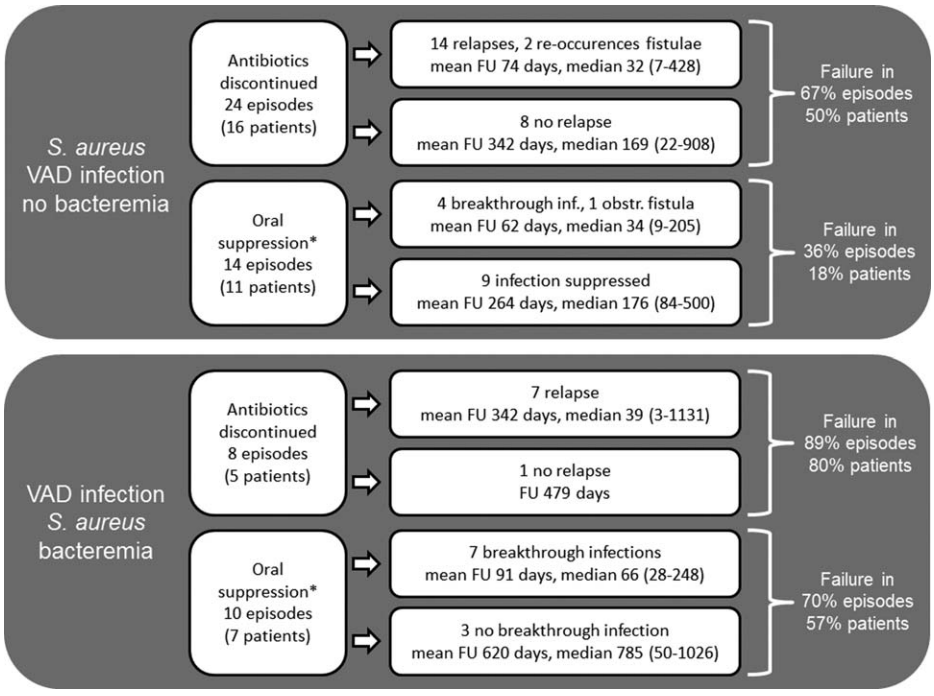

FIG. 2. Outcome of *Staphylococcus aureus* VAD infections under antibiotic suppression therapy. FU: follow-up. Mean FU: follow-up either from (i) discontinuation of antibiotic therapy until relapse, (ii) discontinuation of antibiotic therapy until end of follow-up period, death or heart transplant, (iii) start of oral antibiotic suppression therapy until breakthrough infection, or (iv) start of oral antibiotic suppression therapy until end of follow-up period, death, or heart transplant. *Therapy was considered "suppression therapy" if continued until failure, heart transplant or death from unrelated causes. **In these 11 patients continued suppression was attempted a total of fourteen times: nine times with cephalexin (counting a patient with an obstructed fistula twice), three times with clindamycin (a patient who experienced a rash on clindamycin and was switched to cephalexin was counted as a single episode), once with flucloxacillin, once with ciprofloxacin, and once with moxifloxacin. Eight attempts at suppression with cephalexin and one with ciprofloxacin were successful. ***In these, seven patients continued suppression was attempted a total of ten times: six times with cephalexin, once with cephalexin followed by flucloxacillin and amoxicillin-clavulanate (due to complaints of nausea), twice with clindamycin and once with levofloxacin. Only three treatments with cephalexin were ultimately successful.

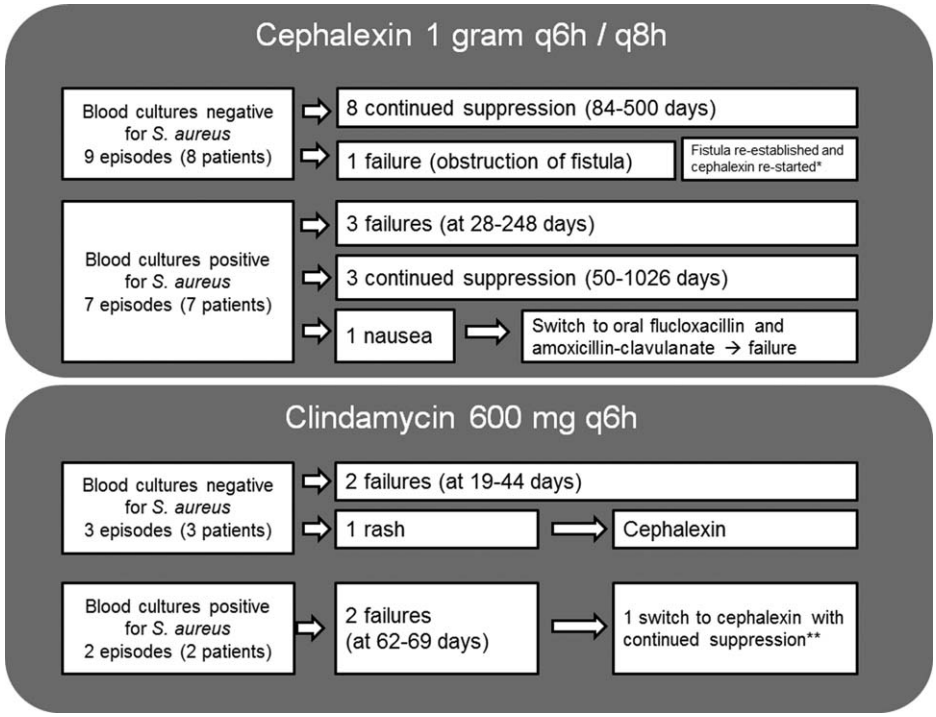

FIG. 3. Outcomes of attempted antibiotic suppression of *Staphylococcus aureus* ventricular assist device infections with cephalexin and clindamycin. *This patient was subsequently counted amongst the nine patients with continued suppression under cephalexin. **In the second patient who failed under clindamycin suppression, at a later stage cephalexin suppression was attempted and failed.

rapidly progressing to death (SAB4 and SAB5). In 10 patients, suppression with oral antibiotics was attempted, with a failure rate of 70% (7/10) (Fig. 2).

Oral antibiotics as suppression therapy

The main antibiotics used as oral suppression therapy were cephalexin and clindamycin (Fig. 3). Only one of the eight patients without *S. aureus* bacteremia receiving continued suppression therapy with cephalexin (1 gram q6h or q8h) had a possible failure, likely due to obstruction of a permanent fistula: the cultures were negative for *S. aureus* and once the fistula was re-established suppression with cephalexin could be successfully continued until heart transplant. Conversely, of the three patients without bacteremia receiving clindamycin suppression (600 mg q8h) two experienced failures; the third developed a rash on clindamycin and was switched to cephalexin.

Seven of the 10 patients with *S. aureus* bacteremia received cephalexin as suppression therapy: three were treated successfully until heart transplant or end of follow-up, three experienced progression of the infection and were switched to intravenous antibiotics, and one developed nausea. The patient who developed nausea was switched to oral flucloxacillin and later to amoxicillin-clavulanate; the infection then progressed and the patient developed *S. aureus* bacteremia. The two patients with *S. aureus* bacteremia receiving clindamycin suppression therapy both had breakthrough infections; in one patient, the infection subsequently responded to oral suppression with cephalexin.

Whole genome sequencing and comparative genome analysis

In all patients from whom multiple isolates were available, these were classified as indistinguishable (<25 allele differences), except for those of patient SAB6 (Fig. 4). In this last patient, the isolate recovered almost 4 years after the last bacteremic episode exhibited 210 allele differences from the prior two isolates. This difference exceeded the cut-off for identical isolates but was not high enough to exclude it being the same strain. The isolates from patient SAB3 differed by 19–20 alleles from that of patient SAB9, suggesting possible cross-transmission.

The antibiotic suppression with levofloxacin in patient SAB2 failed after 3 weeks of treatment. Comparison of the isolates from before (week 35) and after (week 89) this failure demonstrated two mutations in the gene coding for the topoisomerase IV B subunit (*grlB*), which are likely to have caused resistance to levofloxacin, even if phenotypic susceptibility testing did not demonstrate resistance against the fluoroquinolone ciprofloxacin (levofloxacin was not tested).

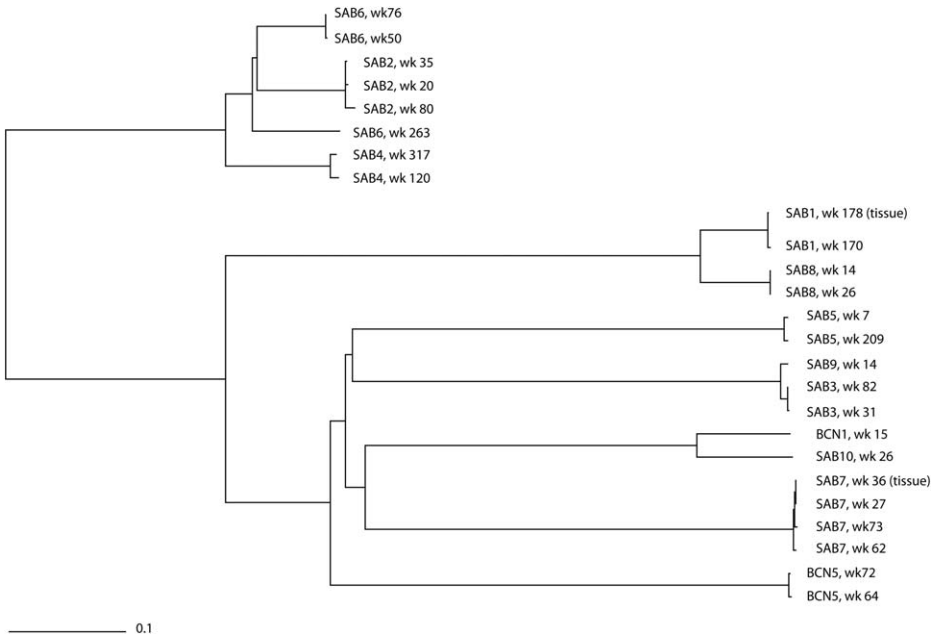

FIG. 4. A cgMLST-based phylogenetic tree of 25 *Staphylococcus aureus* strains recovered from patients with ventricular assist devices. The isolates from patient SAB6 week 50 and 76 differed by only one allele between them but differed by 210 alleles from the isolate from week 263 (isolated almost four years later). The first two isolates can be considered the same, but for the third isolate the relation is unclear. The isolates from patient SAB1 differed by 6 alleles. The three isolates from SAB2 differed by 15 to 16 alleles. The isolates from patient SAB3 showed one difference between them and only 19–20 differences were observed with the isolate SAB9 week 14, suggesting transmission between these two patients. The isolates from SAB 4 differed by 16 alleles. The isolates from patient SAB5 differed by 9 alleles. The four isolates from patient SAB7 differed between 0 and 5 alleles. No allele difference was observed for isolates from SAB8. Only four alleles were different for the two isolates from patient BCN5. Isolates BCN1 week 15 and SAB10 week 26 are unrelated to any of the other isolates.

The isolates that were recovered from patients whose infections progressed under suppression with clindamycin did not acquire new genes or mutations in genes that could explain this failure, although one strain had become phenotypically resistant (patient SAB1, week 178), possibly due to a mutation in a promoter region that was not identified by this analysis.

DISCUSSION AND CONCLUSION

This study found that *S. aureus* VAD infections usually led to complicated, protracted disease, with frequent relapses and often requiring prolonged antibiotic suppression therapy. In 9 of 32 episodes (28%) where antibiotics were discontinued no relapse occurred until the end of the patient follow-up, but this included patients with follow-up of less than a month and a patient who underwent a VAD exchange. Furthermore, relapses could occur up to years after the end of treatment, could progress to bacteremia, and could cause severe sepsis and death: two of the three patients who died from sepsis in this study had recently discontinued their antibiotic therapy. Outcomes were in particular unfavorable in patients who had experienced *S. aureus* bacteremia (relapse in 80% of the patients, 89% of the episodes). Patients with infections limited to the driveline tract had a higher chance of remaining free of relapse until end of follow-up if antibiotics were stopped; 8 of the 16 patients in which this was tried remained free of relapse during their median follow-up of 169 days, suggesting that a single attempt to discontinue therapy in this group could be justified.

Conversely, it was found that continued antibiotic therapy could suppress the infection as long as the VAD was in situ; only in one single patient (SAB7) this was finally not achieved, neither with oral nor with intravenous antibiotic therapy, due to extensive abscess formation of the VAD pocket. The preferred oral regimen for antibiotic suppression was cephalexin 1 gram q6h or q8h. This drug was generally well tolerated and showed higher rates of successful suppression than clindamycin. Furthermore, development of resistance to cephalexin and other first generation cephalosporins is unlikely, even under treatment, as true high-level resistance (i.e., MRSA) requires the acquisition of a complete gene (*mecA* or *mecC*).

Detailed data on the antibiotic treatment of VAD infections is scarce. Jennings et al. described six patients with *S. aureus* driveline infections, one of which also suffered bacteremia, who were treated with antibiotic therapy >6 weeks past the index infection (8). In four patients, the infection could be successfully suppressed with oral antibiotics; these regimens included co-trimoxazole (two patients), cephalexin and dicloxacillin. The authors did not specify the length of suppressive therapy in the individual patients, but for the whole cohort the range was 172 to 1332 days. Two patients experienced failure of their suppressive therapy; they received doxycycline plus ciprofloxacin (failure after 119 days) and doxycycline monotherapy (failure after 135 days). Furthermore, in case reports the use of antibiotic suppression therapy has been described with IV cefazolin (15 months until heart transplant), IV vancomycin (4 months until heart transplant) and linezolid plus rifampicin (6 months until death) (5,9,10).

Infections of foreign materials such as VADs may trigger a reflex to initiate treatment with rifampicin. However, we believe this drug use should be avoided in VAD patients. First of all, its use lacks a rationale: rifampicin has a place in the treatment of prosthetic joint infections only when combined with rigorous debridement and irrigation, and never when a fistula is present, the latter being by definition the case in VAD patients in the form of a driveline tunnel (14). Second, the use of rifampicin will interact with the coumarin anticoagulation therapy which VAD patients receive, potentially leading to life-threatening dysregulations (15).

In our experience, *S. aureus* is by far the most virulent pathogen in VAD infections; the findings in this study can therefore not be extrapolated to all VAD infections. Patients with VAD infections by other micro-organism might benefit from a less aggressive therapeutic approach, accepting colonization or low-grade infections and attempting to discontinue the antibiotic therapy after a limited duration of treatment.

The results of this study should be interpreted with caution: it was retrospective, with a limited number of patients and over the course of the years increasing experience with VAD infections led to different therapeutic approaches, in particular to an increased use of cephalexin suppression therapy. Also, it should be taken into account that the study was conducted in a setting where MRSA was almost nonexistent. These limitations notwithstanding, based on the findings in this study, we suggest cephalexin as first choice treatment for long-term suppression of *S. aureus* VAD infections. Furthermore, in particular in patients who have suffered *S. aureus* bacteremia, we conclude that continued antibiotic suppression therapy is the safest approach as long as a VAD remains in situ.

Funding: No outside funding was received for the preparation of this manuscript. The costs of bacterial sequencing and susceptibility testing were covered by the department of medical microbiology of the UMC Utrecht or were part of routine diagnostics.

Conflict of Interest: None of the authors have any conflict of interest to declare concerning this manuscript.

REFERENCES

1. Nienaber JJ, Kusne S, Riaz T, et al. Mayo Cardiovascular Infections Study Group. Clinical manifestations and management of left ventricular assist device-associated infections. *Clin Infect Dis* 2013;57:1438–48.
2. Gordon RJ, Weinberg AD, Pagani FD, Ventricular Assist Device Infection Study Group, et al. Prospective, multicenter study of ventricular assist device infections. *Circulation* 2013;127:691–702.
3. Tong MZ, Smedira NG, Soltesz EG, et al. Outcomes of heart transplant after left ventricular assist device specific and related infection. *Ann Thorac Surg* 2015;100:1292–7.
4. Roussel LO, Khouri JS, Christiano JG. Pedicled flap closure as an adjunct for infected ventricular assist devices. *Ann Plast Surg* 2017;78:712–6.
5. Sivaratnam K, Duggan JM. Left ventricular assist device infections: three case reports and a review of the literature. *ASAIO J* 2002;48:2–7.
6. Rosenfeldt FL, Kwa LJ, Porapakkham P, et al. Bacteraemia in ventricular assist devices: a common complication that need not affect clinical outcomes. *Heart Lung Circ* 2014;23:234–41.
7. Simon D, Fischer S, Grossman A, et al. Left ventricular assist device-related infection: treatment and outcome. *Clin Infect Dis* 2005;40:1108–15.
8. Jennings DL, Chopra A, Chambers R, Morgan JA. Clinical outcomes associated with chronic antimicrobial suppression therapy in patients with continuous-flow left ventricular assist devices. *Artif Organs* 2014;38:875–9.
9. Tayama E, Arinaga K, Shojima T, et al. Infection management in a patient with a left ventricular assist device: a case report of long-term cefazolin sodium hydrate administration. *J Artif Organs* 2006;9:118–21.
10. Gogas BD, Parissis JT, Iliodromitis EK, et al. Left ventricular assist device vegetation: "cure" without device explantation. *Hellenic J Cardiol* 2010;51:549–51.
11. Bankevich A, Nurk S, Antipov D, et al. SPAdes: a new genome assembly algorithm and its applications to single-cell sequencing. *J Comput Biol* 2012;19:455–77.
12. Seemann T. Prokka: rapid prokaryotic genome annotation. *Bioinformatics* 2014; 30:2068–9.
13. Camacho C, Coulouris G, Avagyan V, et al. BLAST+: architecture and applications. *BMC Bioinformatics* 2009;10:421.
14. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013;56:e1–25.

15. Krajewski KC. Inability to achieve a therapeutic INR value while on concurrent warfarin and rifampin. *J Clin Pharmacol* 2010;50:710–3.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Strains and genes used to build the *Staphylococcus aureus* core genome multi-locus sequence typing (cgMLST) scheme.

Figure S1. Timelines of patients with *Staphylococcus aureus* ventricular assist device (VAD) infections without *S. aureus* bacteremia.

Legend S1. Legend to supporting figure.