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Original article

Oral minocycline as systemic therapy for uncomplicated venous access device-related bloodstream infection with coagulase-negative staphylococci after allogeneic hematopoietic cell transplantation

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ABSTRACT

Background: Venous access device-related bloodstream infection (VAD-BSI) with coagulase-negative staphylococci (CoNS) is a common complication after allogeneic hematopoietic cell transplantation (alloHCT). Standard systemic antimicrobial therapy for uncomplicated VAD-BSI with methicillin-resistant CoNS consists of intravenous (IV) vancomycin (vanco). This requires hospitalization, needs new competent venous access, exposes patients to potential toxicity (mainly renal) and increases the risk of commensal flora dysbiosis with selection of vanco-resistant enterococci. Combined with VAD management (removal or antibiotic locks), oral minocycline (mino) has been evaluated as an alternative systemic therapy for the treatment of uncomplicated VAD-BSIs with CoNS at our center, primarily when the reference treatment with IV vanco was not possible (renal failure or allergy) or when hospitalization was refused by patients. Here, we retrospectively report our single center experience with this mino-based approach.

Patients and methods: From January 2012 to December 2020, 24 uncomplicated VAD-BSIs with CoNS in 23 alloHCT patients were treated with oral mino as systemic antibiotic therapy in combination with VAD management. VAD were implantable ports ($n = 17$), tunneled catheter ($n = 1$) or PIC-lines ($n = 6$). Staphylococci were *S. epidermidis* ($n = 21$) or *S. haemolyticus* ($n = 3$). Mino was administered with a loading dose of 200 mg followed by 100 mg BID for 7–14 days. For 8 VAD-BSIs, patients were initially treated with IV vanco for the first 1–3 days followed by oral mino, while 16 VAD-BSIs were treated with oral mino as the sole antimicrobial agent for systemic therapy. VAD management consisted of catheter removal (for tunneled catheters and PIC-lines, $n = 7$) or antibiotic locks with vanco ($n = 15$) or gentamicin ($n = 2$) administered at least 3 times a week for 14 days (for ports).

Results: Overall, clearance of bacteremia (as assessed by negativity for the same CoNS of surveillance peripheral blood cultures drawn between day+ 3 and +30 after initiation of systemic therapy) was achieved in all but 1 patient (with port) who had persistent bacteremia at day +9. No complication such as suppurative thrombophlebitis, endocarditis, distant foci of infection or BSI-related death was observed in any patient during the 3-month period after initiation of treatment. Regarding the 17 port-BSI cases for which VAD conservative strategy was attempted, failure of 3-month VAD preservation was documented in 7/17 cases and 3-month recurrence of VAD-BSI was observed in 3/17 cases (with 1 patient with cellulitis). Treatment with mino was well tolerated except for a mild skin rash in one patient.

Conclusion: Further prospective studies are needed to evaluate efficacy and safety of this approach.

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Introduction

Recipients of allogeneic hematopoietic stem cell transplantation (alloHCT) often carry long-term venous access devices (VAD), such as peripherally inserted central lines (PIC-lines, inserted via the peripheral vein into the superior vena cava, usually by the way of cephalic and basilar veins), surgically implantable tunneled silicone catheters (e.g., Hickman, Broviac, or Groshong catheters) or subcutaneously implanted port reservoirs (e.g., Ports-A-Cath) [1,2]. In these patients, VAD offer securing central venous access for the administration of chemotherapy, stem cell infusion, supportive therapies (fluids, blood products, parenteral nutrition, antibiotics) and blood draws.

In the USA, more than 5 million long-term VAD are annually inserted in patients with cancer, resulting in 200 000 – 400 000 annual episodes of VAD-related bloodstream infections (VAD-BSI) [1,3]. VAD-BSIs are common complications in patients with hematological malignancies and after alloHCT, because they are fragilized by their immunocompromised status, are exposed to nosocomial infections and receive frequent blood product transfusions [4–10]. VAD-BSIs can be associated with morbidity and mortality, prolonged hospital stays and substantial financial burden [2,4,8,11,12]. A 2013 report estimated that VAD-BSI was the most costly healthcare-associated infection in the USA [12].

Coagulase-negative staphylococci (CoNS) are common bacteria responsible for VAD-BSIs and are often resistant to oxacillin. Compared to VAD-BSIs with *Staphylococcus aureus* or *Candida spp*., VAD-BSIs with CoNS are less often associated with life-threatening complications such as sepsis, endocarditis or visceral abscesses. However, VAD-BSIs with CoNS still result in an increased burden in patient care. The current standard systemic treatment of uncomplicated VAD-BSIs with methicillin-resistant CoNS is IV vancomycin (vanco) for a usual duration of 5 to 14 days (depending on whether the VAD is removed or maintained with salvage antibiotic locks) [1,3,13]. This approach often requires hospitalization and new competent venous access (since the VAD is rendered unusable by the infection), exposes the patient to potential (mainly renal) vanco toxicity [14] and increases the risk of commensal flora dysbiosis with selection of vanco-resistant enterococci [15]. Patients after stem cell transplantation are particularly at risk of iatrogenic and nosocomial complications. In addition, prolonged or repeated hospitalizations can impact their autonomy and quality of life [16,17] and are associated with significant costs and resources consumption for health systems [4,12,18]. The recent experience of the COVID-19 crisis and the saturation of health care has shown the importance of preserving hospital resources. Thus, searching for an outpatient alternative systemic therapy to the reference treatment with IV vanco for uncomplicated CoNS-related VAD-BSI, seemed interesting to our group of investigators.

Minocycline (mino) is an oral antimicrobial agent with strong in vitro activity against most Gram-positive bacteria and potential antibiofilm activity [19–23]. Despite limited clinical data, mino is proposed as an option for some CoNS infections, such as bone and joint infections [24,25]. On a PK/PD point of view, mino has excellent bioavailability [26] and despite its high tissue diffusion, it has been shown that serum levels of mino using standard dosage scheme (200 mg loading dose, then 100 mg BID [26]) are maintained in the range of 2.3–3.5 mg/mL [27], corresponding to more than 4,5–7 fold of the minimum inhibitory concentration (MIC) for the majority of CoNS (which is often $\leq$ 0.5 mg/L). Additionally, this drug is often associated with a favorable safety profile and is inexpensive [26,28–30].

On this basis, systemic therapy with oral mino in combination with VAD treatment (VAD withdrawal or antibiotic locks) has been proposed as an alternative therapy for the management of uncomplicated CoNS-related VAD-BSIs in our center, primarily when standard treatment with IV vanco was not possible (renal failure or allergy) or when patients refused hospitalization. Here, we retrospectively report our single center experience with this mino-based approach for the treatment of uncomplicated VAD-BSIs with CoNS in patients after alloHCT.

Patients and methods

Patient selection

A retrospective analysis was performed on the medical files of patients who received oral mino as systemic therapy for uncomplicated VAD-BSIs with CoNS after alloHCT, at the University Hospital of Liège (CHU de Liège, Belgium), between January 2012 and December 2020. Based on the institutional protocol, oral mino was only proposed for uncomplicated VAD-BSI cases defined as VAD-BSIs occurring in patients with no evidence of sepsis, suppurative thrombophlebitis, endocarditis or septic embolisms and without endovascular or orthopedic material. We further limited the analysis to patients with long-term central VAD (implantable ports, tunneled catheters or PIC-lines; patients with peripheral catheter and short-term central venous catheter being excluded) and VAD-BSI with *S.epidermidis, S. haemolyticus, S. hominis* or *S. capitis.* Patients who had a concurrent infection and received antibiotics with potential anti-CoNS activity during the VAD-BSI episode were also excluded, in order to avoid the influence of these antibiotics on the outcomes.

All patients (or their legal guardians) provided written informed consent for use of protected health data for retrospective research. This study was approved by our institutional ethical committee and was conducted in accordance with the Declaration of Helsinki.

Definition of VAD-BSI and microbiological analyses

VAD-BSIs diagnosis relies on at least 2 positive blood culture samples with the same CoNS (same species and same antibiogram profiles according to the criteria of the European Committee on Antimicrobial Susceptibility Testing [EUCAST]) taken consecutively from the VAD and from a peripheral vein. To limit bias in this retrospective study, differential time to positivity (DTP, delay of positive culture between blood specimens drawn from the VAD and peripherally, respectively) should be at least 2 h to consider VAD-BSI [31]. The diagnosis of VAD-BSI in our institution was optimized by a rigorous standardized pre-analytical procedure for blood cultures collection and incubation, allowing an accurate calculation of DTP (see Supplemental Material). When this procedure was not applied, an "estimated DTP" was calculated retrospectively based on the time of positivity recorded for blood cultures taken from the periphery and from the catheter, but without guaranteeing a reproducible pre-analytical process.

Bacterial genus and species were determined by MALDI-TOF mass spectrometry and antibiograms were performed by using Vitek® 2 automated system [32]. The minimum inhibitory concentration (MIC) of mino was directly tested in antibiogram panels from August 2016. For cultures tested before, the MICs for mino were not available and mino susceptibilities were presumed from the susceptibility results for tetracycline (using EUCAST guidelines) [33].

Oral antibiotic therapy with mino and VAD management

After a loading dose of 200 mg, oral mino was given 100 mg BID for a duration of 5–14 days, depending on whether the VAD was removed (5–7 days) or maintained and treated with antibiotic locks (10–14 days) [1]. Mino could be administered as first line antibiotic therapy or after a short course of a maximum 72 h of IV vanco (pending the antibiogram data confirming mino in vitro susceptibility), left to the discretion of the attending physician.

Associated with systemic therapy, simultaneous VAD-BSI management consisted of either VAD removal or VAD salvage treatment with antibiotic locks. This was left at the discretion of the attending physician, but VAD removal was recommended for non-implanted catheters and in case of signs of local complications per institutional procedure. Antibiotic locks with either vanco or gentamicin were administered at least 3 times a week for 2 weeks, either in a day hospital unit or through

a home nursing facility (with trained nursing teams). No anticoagulant was included in the composition of the locks. The antibiotic concentration of each lock could not be found retrospectively.

Data analyses

Resolution of initial systemic infection was defined retrospectively as a composite outcome integrating the following 3 criteria: 1) the absence of positive subsequent blood culture drawn peripherally, with the same CoNS as the one responsible for the initial episode of VAD-BSI, during the period from day+3 to day+30 after the start of antibiotic therapy; 2) the absence of acute infectious complication possibly linked to the initial episode of VAD-BSI (sepsis, cellulitis, suppurative thrombophlebitis, endocarditis, septic embolism or BSI-related death), occurring during the first month after the start of antibiotic therapy; and 3) the absence of delayed complications possibly linked to the initial episode of VAD-BSI (suppurative thrombophlebitis, endocarditis, deep abscess or BSI-related death), occurring 1 to 3 months after the start of antibiotic therapy or until death, if it occurred from another cause during the follow-up period.

When VAD salvage strategy was attempted, the success rate of VAD preservation was also analyzed. VAD removal events were documented up to 3 months after the start of lock therapy as well as the reason for removal, including as per institutional guidelines 1) uncontrolled systemic infection; 2) failure of VAD decontamination defined as VAD-derived positive blood culture (without bacteriemia in the periphery or clinical symptoms) with the same CoNS as the one responsible for the initial episode of VAD-BSI after the completion of 2 weeks of lock therapy and up to day+30 after their initiation; 3) recurrence of VAD-BSI with the same CoNS (similar antibiogram) within 3 months of starting lock therapy; and 4) local VAD-related complication after the start of lock therapy. It should be noted that there was no standardization either of the frequency or the number of control blood cultures performed after treatment or of the clinical follow-up, due to the retrospective nature of the study.

Safety data were also retrospectively assessed, including the review of any report of allergic manifestation, liver dysfunction, autoimmune disorders, and death of any cause occurring within the first 3 months after initiation of mino therapy.

Results were reported as numbers and proportions (%) with 95 % confidence intervals. No other statistical analysis was performed given the small cohort and the purely descriptive nature of this study.

Results

Characteristics of VAD-BSIs

A total of 24 episodes of VAD-BSIs with CoNS in 23 alloHCT patients were treated with oral mino during the study period. One patient experienced 2 successive independent episodes of VAD-BSIs (the first with *S. epidermidis* and the second with *S. haemolyticus*, having occurred 21 months apart), the first treated with vanco (3 days), oral mino and VAD antibiotic locks and the second with mino and antibiotic locks. The characteristics of these 24 VAD-BSI episodes are summarized in Table 1. The median age of the patients was 52 years old (range 17 to 72). All patients were transplanted for malignant hematological disorders. The median time to onset of VAD-BSI from alloHCT was 101 days (range 19 to 3930). In most cases, immunosuppression was still ongoing at the time of VAD-BSI ($n = 23$). Further, thirteen patients had active acute ($n = 7$) or chronic ($n = 6$) graft-versus-host diseases (GVHD). In addition, one patient had severe neutropenia ($<0.5 \times 10^9$ neutrophils/L) at the time of infection diagnosis.

VAD were implantable ports ($n = 17$), tunneled catheter ($n = 1$) or PIC-lines ($n = 6$). In 16 cases, the diagnosis of VAD-BSI was optimized using a standardized protocol for blood cultures collection and incubation and for the calculation of a precise DTP [31]. For 8 cases, an estimated DTP was calculated retrospectively. Pathogens were *S. epidermidis* ($n = 21$) or *S. haemolyticus* ($n = 3$). In vitro susceptibility to mino was confirmed for 19 CoNS (with a MIC for mino $\leq$ 0.5 mg/L), presumed for 2 CoNS (because of the susceptibility to tetracycline with a MIC $\leq$ 1 mg/L) and unknown for 2 CoNS, (intermediate sensitivity to tetracycline) according to EUCAST guidelines. Finally, in 1 case, the CoNS (*S. epidermidis*) had an intermediate susceptibility to mino (CMI = 1 mg/L) and was resistant to tetracycline (CMI $\geq$ 16 mg/L). All CoNS were resistant to oxacillin (except one *S. epidermidis*) and sensitive to vanco or gentamicin (with a MIC $\leq$ 1 mg/L). No CoNS was resistant to minocycline. (Supplemental data Table S1).

Blood cultures were taken because of general symptoms (fever, chills, asthenia) in 14 cases, minor local signs at VAD site (erythema at the puncture site or weak reflux of the catheter) in 2 cases or for exploration of an isolated biological inflammatory syndrome (asymptomatic patients) in 8 cases. The retrospective review of clinical files in the context of this study enabled us to confirm that no patient presenting

Table 1
Characteristics of patients and VAD-BSI with CoNS and their treatment.

	VAD-BSI with CoNS episodes ($n = 24$)
Clinical context	
Age at diagnosis of infection, median (range), days*	56 (17–72)
Gender*	
Male, *n* (%)	17 (71)
Female, *n* (%)	7 (29)
Conditioning regimen before alloHCT*	
MAC/RIC/ NMA, *n* (%)	10 (42)/9 (37)/5 (21)
Stem cell donor for alloHCT*	
SIB/ MUD/ Haplo, *n* (%)	7 (29)/2 (9)/15 (62)
Time between alloHCT and VAD-BSI, median (range), days	101 (19–3930)
Active acute/ chronic GVHD at diagnosis of VAD-BSI, *n* (%)	7 (29)/6 (25)
Active immunosuppression at diagnosis of VAD-BSI, *n* (%)	23 (96)
Neutropenia (< 0.5 ANC x 10^9/L) at diagnosis of VAD-BSI, *n* (%)	1 (4)
VAD-BSI	
Bacteria	
S. epidermidis/ S.haemolyticus/ S.hominis/ S. capitis, *n* (%)	21 (88)/3 (12)/0 (0)/0 (0)
VAD type	
Implantable port/ tunneled catheter/ PIC-line	17 (71)/1 (4)/6 (25)
Clinical presentation at diagnosis of VAD-BSI	
Asymptomatic, *n* (%)**	8 (34)
Fever, chills, asthenia, *n* (%)	14 (58)
Erythematous puncture site, weak reflux, *n* (%)	2 (8)
Treatment of VAD-BSI	
Systemic antibiotics	
Oral mino monotherapy, *n* (%)	17 (71)
Oral mino after a short (24–72 h) course of IV vanco, *n* (%)	7 (29)
Total duration of systemic treatment, median (range), days	11 (7–23)
VAD treament	
VAD removal, *n* (%)	7 (29)
Vancomycin/ gentamicin locks, *n* (%)	17 (71)

* A total of 24 episodes of VAD-BSIs with CoNS occurred in 23 alloHCT patients. One patient experienced 2 VAD-BSI. For that one, data on patient related-characteristic were duplicated to allow presentation on a basis of 24 VAD-BSI events.

** Blood cultures drawn in the context of exploration of isolated biological inflammatory syndrome.

***In one case, antibiotic locks frequency was unknown.

CoNS refers to coagulase-negative staphylococci; GVHD, graft-versus-host disease; Haplo, HLA-haploidentical related donor; MAC, myeloablative conditioning; Mino, minocycline; MUD, HLA-matched unrelated donor; NMA, non-myeloablative conditioning; RIC, reduced-intensity conditioning; SIB, HLA-identical sibling donor; VAD, venous access device; VAD-BSI, Venous access device-related bloodstream infection.

with signs of complicated VAD-BSI or carrying an endovascular or prosthetic device had been treated with mino, in accordance with the institutional protocol.

Management of VAD-BSI

All VAD-BSI were treated with systemic antibiotic therapy combined with VAD management. Treatment modalities are summarized in Table 1 and Fig. 1. Among the 24 VAD-BSI, 17 (71 %) were immediately treated with oral mino as the only systemic therapy, while 7 (29 %) received initial treatment with IV vanco for the first 24–72 h before switching to oral mino. The duration of systemic treatment was 7–14 days in most cases ($n = 21$), except for 2 cases for which the treatment was continued longer (respectively 21 and 23 days, for unknown reasons) and 1 case for which the duration of treatment could not be verified retrospectively.

VAD management consisted of catheter removal (for tunneled and PIC-lines, $n = 7$) or antibiotic locks (for ports) with vanco ($n = 15$) or gentamicin ($n = 2$) for 2 weeks (Table 1 and Fig. 1). The frequency of administration of antibiotic locks was heterogeneous and varied according to the hospital or ambulatory nature of the care: the antibiotic locks were performed daily in inpatient setting ($n = 3$) while they were performed 3 times a week in outpatient setting ($n = 13$). For 1 other case (with vanco locks), the frequency of administration could not be found retrospectively.

Resolution of systemic infection

Regarding resolution of systemic infection, our strategy of combining oral mino (+/- max 24–72 h vanco) with VAD management (removal of antibiotic locks) was associated with the clearance of bacteremia in the periphery in 23 of the 24 cases of VAD-BSIs with CoNS (Table 2). One death occurred 7 weeks after initiation of mino therapy (in a patient with a PIC-line, treated with mino alone and VAD removal), due to steroid-refractory GVHD as primary cause of death. In this case, clearance of CoNS bacteriemia was achieved and death was considered not related to VAD-BSI infection. No acute or delayed VAD-BSI related complication was observed during the surveillance period until 3 months after starting antibiotic treatment or until death. Overall, this corresponds to an overall success rate of 96 % (95 % confidence interval [CI], 79–99 %), according to our composite outcome definition (Table 2 and Fig. 1A).

The only case of treatment failure concerned a port-BSI with *S. epidermidis* which was treated with mino as the sole systemic therapy and VAD locks with vanco. In this case, bacteremia in the periphery was persistent by day +9 after the start of mino and required catheter

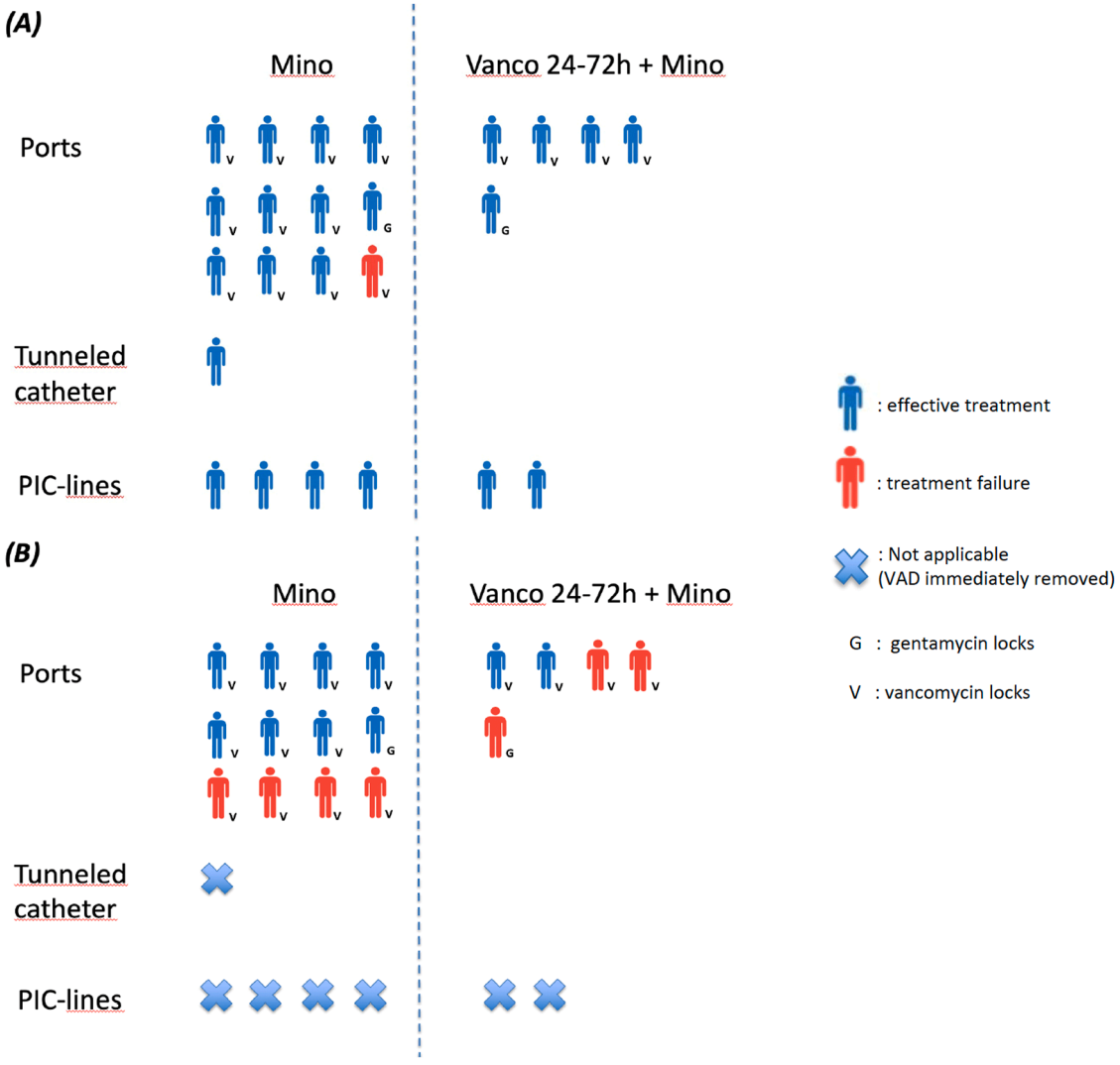

Fig. 1. Efficacy of oral mino (+/− 24–72 h vanco) combined with VAD removal or antibiotic locks for uncomplicated VAD-BSI with CoNS: (A) resolution of systemic infection and (B) VAD preservation.

Table 2
Outcomes of the cohort: synthesis of treatment failure.

	All episodes of VAD-BSI $n = 24$	Implantable ports: Mino + VAD antibiotic locks $n = 17$	Tunneled/PIC-lines: Mino + VAD removal $n = 7$
Resolution of systemic infection			
Failure	1	1	0
Causes of failure:			
Positive peripheral blood culture(s) (from day +3 to +30 after starting mino)	1	1	0
Acute complication[1] (<1 month after mino)	0	0	0
Delayed complication[1] (1–3 months after mino)[*]	0	0	0
VAD preservation strategy for ports			
Port removal	–	7	NA[2]
Causes of removal:			
Uncontrolled systemic infection	–	1	NA[2]
Failure of VAD decontamination	–	3	NA[2]
Recurrence of VAD-BSI (<3 months after lock therapy)	–	3[§]	NA[2]
VAD local complication (<3 months after lock therapy)	–	1[§]	NA[2]

[1] Complication possibly related to the initial CoNS bacteremia: sepsis, cellulitis, suppurative thrombophlebitis, endocarditis, septic embolism or BSI-related death.

[2] NA: not applicable (VAD immediately removed; no VAD conservative strategy attempted).

[*] 1 death occurred 7 weeks after initiation of mino therapy, due to steroid-refractory GVHD as primary cause of death. In this case, clearance of CoNS bacteriemia was achieved and death was considered not related to VAD-BSI infection.

[§] 1 case of recurrent VAD-BSI was complicated by cellulitis at the site of the implantable port (same case).

#1 port was removed early during the initial VAD-BSI episode due to persistent bacteremia

Mino refers to minocycline; VAD, venous-access device; VAD-BSI, venous-access device bloodstream infection.

removal and systemic IV vanco therapy.

It should be noted that in the peculiar case of VAD-BSI with *S.epidermidis* with an intermediate in vitro susceptibility to mino, sterilization of the blood cultures (both taken peripherally and derived from the port) was obtained and the VAD was preserved.

VAD preservation strategy for ports

For the 17 port-BSI cases, VAD preservation strategy with systemic antibiotic therapy (oral mino +/- vanco) coupled vanco/gentamicin VAD locks was attempted. This strategy failed to control systemic infection in 1 case (see above). Failure of VAD decontamination at completion of lock therapy was observed in 3 cases and delayed (1–3 months) recurrence of VAD-BSI with the same CoNS was reported in 3 cases (with 1 patient presenting with cellulitis at the site of port when BSI recurred) (Table 2 and Fig. 1B). All these events led to VAD removal. This corresponds to a VAD preservation rate of 59 % (95 % CI, 36–78 %).

Safety of oral mino

Treatment with oral mino was well tolerated except a mild skin rash in one patient, which was treated with topical corticosteroids. No hepatic toxicity was noted. No early discontinuation of mino therapy was reported due to side effects attributed to mino. There was no evidence of new diagnosis or worsening of autoimmune diseases within the 3 months after mino therapy. Occurrence or worsening of GVHD within 3 months of starting mino therapy was observed in 3 cases (1 progression of a pre-existing acute GVHD, 1 novel diagnosis of acute GVHD and 1 novel diagnosis of chronic GVHD), but causality with mino could not be determined. One death occurred within the 3 months after mino therapy (7 weeks after initiation of mino therapy associated with PIC-line removal) due to steroid-refractory GVHD as primary cause of death.

Discussion

To the best of our knowledge, this is the first retrospective case series of uncomplicated VAD-BSI with CoNS in patients after alloHCT treated with oral mino (alone or after a short course of 24–72 h IV vanco) as systemic therapy in combination with VAD management (removal or antibiotic locks).

From our point of view, it is important to continue to investigate outpatient management strategies for non-severe complications after alloHCT. Limiting the number and duration of hospital stays for these heavily pretreated patients could have a beneficial impact on their quality of life [16,17], on reducing the risk of nosocomial infections and, overall, on the preservation of financial and logistical resources of health-care systems [18,34]. Hence, evaluating oral alternatives to the reference treatment with IV vanco for systemic therapy for uncomplicated CoNS-related VAD-BSI is an interesting field of investigation. Antibiotics other than mino are also known to have anti-CoNS activity and good oral bioavailability, such as linezolid and trimethoprim-sulfamethoxazole (TMP-SMX) [35,36]. However, both drugs (at therapeutic doses) are often avoided in the context of post-alloHCT, as a precaution due to the risk of hematological and/or renal toxicities. Moreover, the antibacterial spectrum of TMP-SMX is also broader compared to mino and it could therefore be more at risk of inducing dysbiosis of the commensal flora in these fragile patients. Finally, the cost of linezolid is currently much higher than that of mino.

In our single-center retrospective analysis, resolution of systemic infection was observed in 23/24 cases using an oral mino-based approach combined VAD management (removal or antibiotic locks) and this treatment appeared to be well tolerated. However, given its retrospective nature, absence of a control group and the small size and heterogeneity of the cohort, no conclusion can be drawn on the efficacy of mino *per se* from our study. In particular, the heterogeneity in terms of catheter management (ablation or conservation) and systemic antibiotic therapy (mino alone or after a short course of 24–72 h of IV vanco) may have played a confounding role and influenced the results.

The majority of VAD-BSIs in our study involved implantable ports (17 cases, 71 %). The 7 other cases were tunneled VAD or PIC-lines and management of these cases combined oral mino to catheter removal. When the catheter is removed, some investigators have suggested that systemic antibiotic therapy might even be omitted in uncomplicated VAD-BSIs with CoNS, with close monitoring by repeated blood cultures to confirm the absence of bacteremia. In a retrospective analysis, Hebeisen et al. compared the evolution of untreated cases ($n = 32$) with those treated with systemic antibiotic therapy (vanco in 90 % of cases, $n = 140$) after catheter removal and observed no episodes of persistent or recurrent BSI in the untreated group [37]. Recently, a randomized multicenter non-inferiority clinical trial was initiated to compare the two options (5–7 days of antibiotic therapy versus omission of antibiotics and surveillance after catheter removal) in uncomplicated catheter-related BSI with CoNS and in immunocompetent patients [38]. Unfortunately, this study was stopped due insufficient recruitment. Currently, the two options are both validated according to the Infectious Diseases Society of America (IDSA) guidelines for the general population [1]. Therefore, it is possible that the 7 cases where the VAD was removed have driven favorable outcomes in our cohort.

For 7 of our 24 cases, initial antibiotic therapy with IV vanco was administered during the first 24 to 72 h before switching to oral mino.

Due to the small size of our cohort and only 1 episode of persistent bacteremia, it was not possible to determine to what extent this prior vanco treatment might have influenced our results. The only case of persistent bacteriemia observed was in a patient treated with mino alone as systemic therapy. However, mino as single systemic therapy combined with VAD management was effective in controlling systemic infection in another 16/17 other cases (5/5 with mino alone after VAD removal and 11/12 with mino alone and VAD antibiotic locks). Moreover, the strategy of an initial treatment with a short course of vanco followed by a rapid switch to oral mino might still allow a vanco-related toxicity sparing approach and would limit length of hospital stay, compared to standard treatment with IV vanco for 5 to 14 days.

Further prospective studies are needed to assess the efficacy and safety of this mino-based approach as systemic therapy for uncomplicated VAD-BSI with CoNS. Waiting for these, caution should be exercised when using an unvalidated approach for the treatment of VAD-BSI with CoNS and rapid switching to another antibiotic (e.g. standard IV vanco therapy) should be performed in the cases of persistent bacteremia identified on control blood cultures. In our study, bacteremia was persistent after the start of mino in 1 case (port-BSI with *S. epidermidis*, treated directly with oral mino and VAD locks with vanco), and required catheter removal and systemic IV vanco rescue therapy.

Regarding the 17 port-BSI cases for which VAD conservative strategy was attempted, failure of 3-month VAD preservation was documented in 7/17 cases and 3-month recurrence of VAD-BSI was observed in 3/17 cases. These proportions are in line with the outcomes reported by other groups when using VAD conservative approach [39–43]. therapy in combination with systemic antimicrobials is currently recommended by most experts when the decision of VAD preservation is retained, the choice of antibiotic, its concentration, the benefit of adding anticoagulants (heparin, EDTA or citrate) and the duration of catheter therapy do not reach a consensus [1,3,13,41,44]. In our study, modalities of antibiotic locks mostly consist of vanco solution administered at least 3 times a week and no anticoagulant was added. Recently, Alonso et al. have specifically assessed vanco lock therapy in combination with systemic antimicrobials in 76 staphylococcal (85 % CoNS) long-term catheters BSI and reported a success rate of 3-month catheter retention of 42 % [43]. Vanco is the most commonly used antibiotic for lock therapy. However, it was reported to have a limited activity against organisms embedded in a biofilm [45,46].

Several approaches are under investigation to improve rates of VAD preservation in case of CoNS associated VAD-BSI. Several studies have suggested a better diffusion of daptomycin inside staphylococcal biofilm and higher rate of CoNS eradication from catheters compared with vanco [47–49]). Recently, some clinical retrospective studies have reported high proportion of VAD preservation when using daptomycin locks (76% at 30 days [50] or daptomycin + taurolidine locks (95 % at 30 days [51]) in patients with CoNS associated VAD-BSI. Mino has also displayed eradication potential against bacteria embedded in a biofilm on a catheter surface [19,22,23] and a prospective pilot clinical study patients showed promising results by using a mino-EDTA-ethanol lock solution to salvage indwelling VAD in cancer patients with VAD-BSI due to various organisms [52].

Conclusion

To the best of our knowledge, this is the first case series of uncomplicated VAD-BSI with CoNS in patients after alloHCT treated with oral mino as systemic antimicrobial therapy in combination with VAD removal or antibiotic locks. However, given the retrospective nature, the absence of a control group, the small size and the heterogeneity of the cohort, no conclusion can be drawn on efficacy and safety from our study. Further prospective studies are needed to evaluate this approach. If shown to be safe and effective in the future, the interest of this approach would be to provide a low-cost and orally administered alternative to the reference treatment with IV vanco.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.retram.2023.103422.

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