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CLINICAL THERAPEUTICS

In Vivo Effectiveness of Several Antimicrobial Locks To Eradicate Intravascular Catheter Coagulase-Negative Staphylococci Biofilms

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ABSTRACT Tunneled central venous catheter (TCVC) related infection remains a challenge in the care of hemodialysis patients. We aimed to determine the best antimicrobial lock therapy (ALT) to eradicate coagulase-negative staphylococci (CoNS) biofilms. We studied the colonization status of the catheter every 30 days by quantitative blood cultures (QBC) drawn through all catheter lumens. Those patients with a significant culture (i.e.,100 to 1,000 CFU/mL) of a CoNS were classified as patients with a high risk of developing catheter-related bloodstream infections (CRBSI). They were assigned to receive daptomycin, vancomycin, teicoplanin lock solution, or the standard of care (SoC) (i.e., heparin lock). The primary endpoint was to compare eradication ability (i.e., negative QBC for 30 days after ending ALT) rates between different locks and the SoC. A second objective was to analyze the correlation between ALT exposure and isolation of CoNS with antimicrobial resistance. Daptomycin lock was associated with a significant higher eradication success than with the SoC: 85% versus 30% (relative risk [RR] = 14, 95% confidence interval [CI] = 2.4 – 82.7); followed by teicoplanin locks with a 83.3% success (RR = 11.7; 95% CI = 2 – 70.2). We observed CoNs isolates with a higher teicoplanin MIC in patients with repeated teicoplanin locks exposure (coefficient = 0.3; 95% CI = 0.11 – 0.47). However, teicoplanin MICs decreased in patients treated with vancomycin locks (coefficient = −0.56; 95% CI = −0.85 – −0.02). Methicillin-resistance decreased with accumulative ALT (RR = 0.82; 95% CI = 0.69 – 0.98). In this study, daptomycin locks achieve the highest eradication rate of CoNS from hemodialysis catheters *in vivo*.

KEYWORDS biofilm, tunneled central venous catheter, hemodialysis, catheter-related bloodstream infection, coagulase-negative staphylococci

According to the United States Renal Data System, 80% of patients in 2018 began hemodialysis through a tunneled central venous catheter (TCVC) despite arteriovenous fistulas and grafts having long been preferred as the best vascular access (1). In Spain, there is no official data about TCVC in this set of patients, but the 2020 Catalan Renal Registry reported that 32.2% of patients had a TCVC (2). Catheter-related bacteremia is one of the most common causes of mortality in hemodialysis (HD) patients (1, 3) and a significant cause of morbidity and economic burden in this population (4, 5). The microorganisms most frequently involved are coagulase-negative staphylococci (CoNS) (4, 6, 7). Some authors have shown the usefulness of antibiotic lock therapy (ALT) and its superiority over antiseptic locks in the treatment of catheter-related

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TABLE 1 Participants' demographics and clinical characteristics at baseline[a]

Patients (n = 21)	Value
Age (yrs), median (IQR)	70 (57.5–78)
Gender (male), no. (%)	7 (33.33)
Charlson score, median (IQR)	7 (5−8)
Body mass index (kg/m^2), median (IQR)	22.7 (20.5–24.2)
Systolic blood pressure (mm Hg), median (IQR)	118 (81–135)
Diastolic blood pressure (mm Hg), median (IQR)	60 (51–70.5)
Albumin (g/dL), median (IQR)	3.2 (2.67–3.71)
Duration of hemodialysis (mo), median (IQR)	35.67 (15.61–73.22)

[a]IQR: interquartile range; no: number.

bloodstream infections (CRBSI) (4, 8–10). ALT and systemic antibiotics are recommended for managing CRBSI with catheter retention when CoNS are involved (7, 11). Some studies have proposed antimicrobial lock prophylaxis in hospitals with high rates of catheter-related infections (6, 12, 13). However, this approach is challenging due to the potential emergence of antimicrobial resistance and side effects.

On the other hand, several studies have tried to determine the best antimicrobial to eradicate *in vivo* biofilms, but without consensus due to the lack of head-to-head comparison studies (14). This study selected nonbacteremic patients with colonized catheters in a hemodialysis population. It aimed to compare different *in vivo* antimicrobial lock solutions with the standard of care (SoC) (i.e., heparin locks) to determine the most efficacious solution to eradicate CoNS biofilms within the TCVC.

RESULTS

Patient characteristics. Most patients were women (66.7%) with a median Charlson comorbidity index of 7. The median body mass index was 22.7 kg/m^2 (IQR 20.5–24.2), with median serum albumin below the normal range (i.e., 3.2g/dL, IQR 2.8–3.7). The median time in the hemodialysis program before inclusion in the study was 3 years (IQR 1.3–6.1) (see Table 1).

The three leading causes of end-stage renal disease were diabetic kidney disease (23.8%), polycystic nephropathy (23.8%), and glomerulonephritis (14.3%).

In our study, we followed patients until death in 71.4% of the cases. No death was related to infection or adverse events related to ALT. The median time from CCC to death was 36.4 months (IQR 14.5–60.3). Median catheter life span until the first CCC was 33.6 months (IQR 17.7–66). The most common coagulase-negative staphylococci isolated from CCC episodes was *S. epidermidis* (78%).

There was a statistically significant difference between treatment groups. Patients with a CCC episode treated with daptomycin locks achieved the highest success rate (85%), followed by teicoplanin (83.3%) and vancomycin locks (61.5%). In comparison, only 30% of the CCC episodes managed with the Standard of Care keep sterile QBC for 30 days (Table 2). There were no statistically significant differences between the treatment groups regarding catheter malfunction (P = 0.24). No patients with catheter malfunction had CRBSI within 30 days. There were no statistically significant differences in doses of antibiotics or length of therapy between experimental groups (i.e., all patients received between 9 – 10 locks within 17 to 21 days). We did not observe statistically

TABLE 2 Distribution of outcomes, treatment characteristics, and time at risk by therapy groups[a]

Characteristic	Teicoplanin lock (n = 12)	Daptomycin lock (n = 14)	Vancomycin lock (n = 13)	Standard of care (n = 20)	P value
Success, no. (%)	10 (83.3)	12 (85.7)	8 (61.5)	6 (30)	0.003*
Catheter malfunction, no.	2 (16.7)	0 (0)	2 (15.4)	9 (25)	0.24*
Doses of antibiotics, median (IQR)	9 (9–10)	9 (9–10)	9 (9–10)		0.53**
Length of treatment (days), median (IQR)	20 (17–21)	19 (18–21)	20 (19–21)		0.83**
Catheter lifespan (yrs), median (IQR)	2.21 (0.5 – 3.65)	2.64 (1.65 – 6.75)	5.13 (4.54 – 5.65)	2.27 (1.52 – 5.49)	0.15**
Hemodialysis vintage (yrs), median (IQR)	3.14 (1.15 – 4)	9.14 (5.13 – 10.1)	5.39 (4.88 – 9.45)	3.17 (1.73 – 6.57)	0.003**

[a]IQR, interquartile range; *, Fisher's exact test; **, Kruskal-Wallis test.

TABLE 3 Relevant MIC values (MIC_{50} and MIC_{90}) for the experimental antibiotics of the isolated microorganisms[a]

	Teicoplanin		Vancomycin		Daptomycin	
Microorganism	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
S. epidermidis	4	16	2	4	0.5	2
S. haemolyticus	2	4	0.25	1	0.06	0.25
S. hominis	0.25	0.25	0.25	0.25	0.06	0.06
S. warnerii	4	4	1	4	0.5	1

[a]MIC_{50}: MIC required to inhibit the growth of 50% of microorganisms (mg/mL).

significant differences in the life span of the catheter among the treatment groups. We show MIC50 and MIC90 for each antimicrobial in Table 3.

Primary endpoint. As shown in Fig. 1, daptomycin locks were significantly more effective at maintaining eradication for 30 days compared with SoC (RR 14 95% CI = 2.4–82.7; $P = 0.004$), followed by teicoplanin locks with RR 11.7 (95% CI = 2–70.18; $P = 0.007$). There were no statistically significant differences between vancomycin locks and SoC (RR = 3.7; 95% CI = 0.9–16.3; $P = 0.079$).

Secondary endpoint. There was a moderate positive correlation between the number of previous CCCs treated with teicoplanin and CoNS isolates teicoplanin MICs (coefficient 0.3; 95% CI = 0.1–0.5; $P = 0.002$) (Fig. 2). However, this increase did not change the interpretation according to breakpoints.

On the other hand, we found a moderate negative correlation between the number of days of vancomycin lock therapy and teicoplanin MICs (coefficient −0.6; 95% CI = −0.9 to −0.02; $P = 0.046$). Regarding CoNS methicillin resistance emergence, we described a discrete inverse relationship with the number of previous antibiotic lock treatments (RR 0.82; 95% CI = 0.69–0.98; $P = 0.031$) (see supplementary S1 for more information). We found no correlations for the other antibiotics (see supplementary S2 and S3 for more information).

DISCUSSION

The present study shows that daptomycin and teicoplanin locks effectively eradicate CoNS biofilms within a TCVC. Compared with the SoC, a lock solution with 5 mg/mL of daptomycin combined with 500 IU of heparin makes CCC eradication 14 times more likely. In contrast, eradication with teicoplanin locks proved to be 11.7 times more likely. The difference in eradication between vancomycin and the SoC was not statistically significant. Although we found no difference between SoC and Vancomycin locks for CCC eradication, Alonso et al. (4), in patients with CRBSI, described better results with systemic therapy and vancomycin locks than with systemic treatment and oxacillin/teicoplanin locks. However, a more extensive meta-analysis by Fang-Ping Dang et al. found worse results with vancomycin locks than with the SoC (5), as our study shows.

Some meta-analyses have attempted to identify the most effective antimicrobial lock solution with contradictory results. However, none included randomized control trials

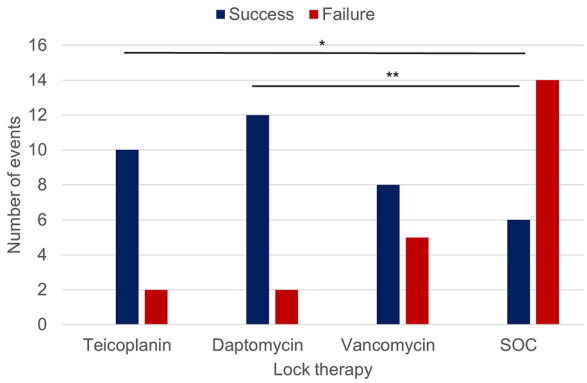

FIG 1 Outcomes in the treatment groups as determined by negative quantitative blood culture for 30 days.

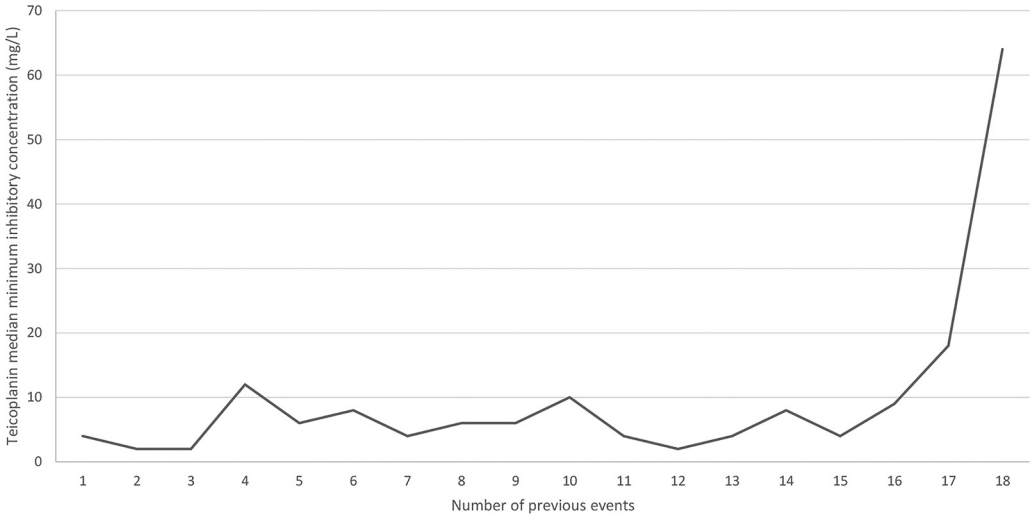

FIG 2 Evolution of the Teicoplanin median MIC relying on the number of previous events.

that allowed the comparison of daptomycin with teicoplanin (5, 15). Our better results with daptomycin are consistent with other *in vitro* findings, which described a better daptomycin diffusion inside staphylococcal biofilms compared with vancomycin (16, 17).

In vitro studies by LaPlante et al. and Bookstaver et al. (18, 19) demonstrated the usefulness of Vancomycin and Daptomycin locks on an immature biofilm model. Although our sample size made it difficult to find significant differences with Vancomycin locks, it is also possible that the discrepancy in the results may be due to an early recurrence of colonization in patients treated with Vancomycin.

In the study by Bookstaver et al. (19) the catheters were incubated for a maximum of 24 h, which represents a limitation because patients usually undergo hemodialysis three times per week. This model does not allow the evaluation of early relapses due to the loss of viability of the substance used.

On the other hand, the study by LaPlante et al. (18) in the eradication model uses catheters with a 24-h incubation biofilm, making it possible to evaluate the antimicrobial action on an immature biofilm but not its effect on an established biofilm where eradication is more complex. These differences inherent to the comparison of *in vitro* models with real-world studies could explain part of the differences in our results.

We found an increase of CoNS isolates with higher MIC for teicoplanin in patients with repeated CCC treated with teicoplanin locks, possibly because repeated antibiotic exposure could lead to the selection of microorganisms with lower sensitivity to antimicrobials. Bueloni et al. reported similar findings; they described a statistically significant difference between gentamicin-cefazolin and taurolidine lock (38.7% versus 5%) of Gram-positive methicillin-resistance in exit-site infection (20), probably for repeated exposition to antimicrobials.

Considering the potential for antimicrobial resistance with the indiscriminate use of ALT and the impact on the morbidity and mortality of patients with CRBSI, we believe that the most rational approach is to select the patients who will benefit most from lock therapy. Consistent with our views, Brañas et al. showed a decrease in the CRBSI rate by culture-guided decolonization with ALT and did not report antimicrobial resistance isolates (21).

In addition, an unexpected finding was that with longer vancomycin locks treatments, subsequent CoNS isolates in that catheter showed lower MIC for teicoplanin. This finding suggested that a more prolonged vancomycin exposure in the catheter's lumen might increase its diffusion inside the biofilm, improving its bactericidal effect (16).

Another interesting finding was an 18% decrease in the probability of methicillin-resistant CoNS isolation for each previous episode treated with ALT. According to these

data, we could infer that this phenomenon might be related to the seesaw effect. Previous *in vitro* studies described this phenomenon for *S. aureus* and *S. haemolyticus* (22–24). Renzoni et al. suggested that glycopeptides and lipopeptides induce mutations in mprF handling dysfunction of the PrsA protein, which is anchored in the cellular wall and necessary for the maturation of Penicillin-binding protein 2a (PBP2a). This decreases levels of PBP2a and increases sensitivity to beta-lactams while increasing resistance to glycopeptides and daptomycin (25). Barber et al. described the seesaw effect using teicoplanin (26), which is consistent with our results.

The limitations of our study are inherent to the fact that we give a recommendation to the patient's attending physicians, and they decided on the final treatment, which may have led to a selection bias such that patients with a higher risk of poor evolution received antimicrobial treatment. Despite this, our study showed that daptomycin and teicoplanin were more efficient in eradicating a CCC episode. Our study had a small number of patients treated in each group; small studies could overestimate the magnitude of associations. More extensive studies are needed. Changes in the MIC of the different antibiotics should be interpreted with caution, considering the length of the study and the possibility of natural epidemiological changes.

In this study, of hemodialysis patients with TCVC, daptomycin-heparin and teicoplanin-heparin lock solutions proved to be the effective therapy to achieve microbiological eradication of catheter critical colonization compared with Vancomycin and the SoC.

MATERIALS AND METHODS

We conducted a prospective pilot study at the Clinica Universidad de Navarra hemodialysis, a 300-bed University Hospital in Pamplona, Spain. The hemodialysis unit serves an average of 44 patients, 22 patients per day, with 11 dialysis machines divided into two shifts for patient care. From March 2005 to May 2019, we included in the protocol all consecutive adult patients in regular hemodialysis program with a TCVC. Our institution performs surveillance QBC as part of the routine quality infection control program. We extracted 10 mL of blood through each catheter lumen every 30 days and processed cultures by the lysis-centrifugation method (Isolator system; Wampole Laboratories, Cranbury, NJ). We identified isolated microorganisms by using standard techniques. We performed antimicrobial susceptibility testing using concentration gradient strips and the Vitek2 antimicrobial susceptibility test system

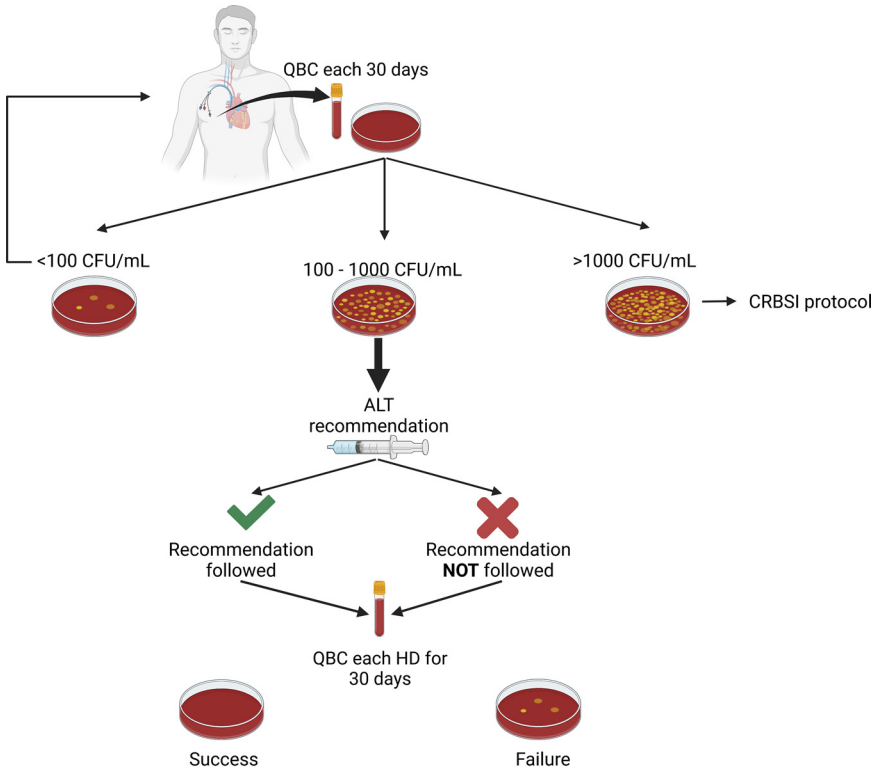

FIG 3 Infection control surveillance algorithm.

TABLE 4 Composition of the lock solutions used in the study

Antimicrobial	Concn (mg/mL)	Sodium heparin concn (UI)
Teicoplanin	10	500
Daptomycin	5	500
Vancomycin	10	100
Standard of care		5,000

(bioMérieux) following the most current European Committee on Antimicrobial Susceptible Testing recommendations. From 2005 to 2010, we used the Clinical & Laboratory Standards Institute recommendations (27–29). The ethics committee of Navarra approved the study.

Based on previous studies (30), we defined a Critical Catheter Colonization (CCC) as the isolation of 100 to 1,000 CFU/mL of a CoNS (except for *S. lugdunensis*). According to Ibeas et al., a patient with a CCC has a high risk of developing CRBSI (31). Infectious disease consultants recommended antimicrobial treatment based on the antimicrobial susceptibility test and the best scientific evidence available at the time of recommendation (Fig. 3). For this reason, in the program's first years, we used vancomycin locks, later teicoplanin locks, and finally daptomycin locks (16, 32).

When Daptomycin locks was used, we reconstitute the vial with lactated Ringer's solution, for the other locks we reconstituted the solution with 0.9% sodium chloride solution. We instilled 5 mL locks at the end of every hemodialysis session. Locks were administered for 21 days (9 HD sessions) based on national guidelines (31). Table 4 shows the composition of the different lock solutions.

We considered biofilm eradication successful when the patient had negatives QBCs for 30 days after ALT completion.

Among the 149 patients, we identified 59 episodes of CCC due to CoNS. We treated 39 episodes with antibiotic lock therapy and 20 with SoC (i.e., 5,000 IU of Hibor [Bemiparin sodium]).

We performed all analyses per protocol using SPSS software (version 26.0). We used nonparametric tests due to the sample size and the absence of normality. We compared the eradication ability of the different lock solutions and catheter malfunctions incidence (blood pump speed $<$300ml/min) with Fisher's exact test. To estimate the treatment success for each antibiotic, we used logistic regression. We also correlated the MIC for each antibiotic and the accumulative number of episodes, length of therapy, and the number of doses with Spearman's rank correlation coefficient. We calculate the confidence interval for the correlation based on a previous study by Santabarbara (33). *P*-values $<$ 0.05 were considered statistically significant.

Data availability. The data that support the findings of this study are available at https://doi.org/10.6084/m9.figshare.21547893.v2.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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