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Treatment of long-term catheter-related bloodstream infections with short-course Daptomycin lock and systemic therapy associated with Taurolidine-lock: A multicenter experience

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Abstract

Purpose: Few studies describe the efficacy of antibiotic lock therapy (ALT) in long-term catheter-related bloodstream (CRBSI) infections. We applied local protocols combining Daptomycin (DPT) and Taurolidine ALT, associated with systemic antibiotic treatment (SAT), for conservative management of coagulase-negative Staphylococci (CoNS) CRBSI.
Methods: Patients admitted for CoNS-associated CRBSI and treated with DPT and Taurolidine as ALT were retrospectively analyzed. Success was defined as catheter retention 30 days after ending treatment. Catheter removal within 30 days was considered as failure.
Results: From April 2018 to September 2021, 22 subjects with CoNS-associated-CRBSI were included (95% with cancer, mean age 64 years, 59% male). *Staphylococcus epidermidis* was isolated in 82% of cases. Mean duration of DPT was 3.9 and 3 days as ALT and SAT, respectively. SAT also included Rifampin for 3 days. Taurolidine ALT was started on day 4 and was combined with oral SAT, that is, either Linezolid or Tedizolid. Mean duration of Taurolidine was 10.5 days, while total antibiotic treatment lasted 13.5 days. Clinical success and failure rates were 95% and 5%, respectively.
Discussion: Short course DPT as ALT, combined with SAT and Taurolidine ALT, allowed high rates of conservative management of catheters in case of CoNS-associated-CRBSI.

Keywords

Catheter-related bloodstream infection, coagulase negative *Staphylococci*, lock therapy, Daptomycin, Taurolodine

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Introduction

Long-term in-dwelling catheters are frequently used devices, in particular for chemotherapy and parenteral nutrition. Catheter-related bloodstream infections (CRBSI) are frequent complications and can increase morbidity, mortality, and costs.[1–4]

While catheter removal is generally required for treating CRBSI, salvage therapies for conservative management of the catheter have been suggested.[5] Indeed, catheter removal has been associated with potential increases on costs and significant delays in treatment, especially in cancer patients.[6] Therefore, main guidelines recommend a conservative management of uncomplicated CRSBI due to coagulase-negative staphylococci (CoNS), which represent the most frequent pathogens associated.[5,6] To improve success rates, antimicrobial lock

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therapy (ALT) is required in association with parenteral antibiotic treatment. ALT consists of instilling an antimicrobial solution in the catheter hub, thus allowing to achieve *in situ* concentrations many-fold higher than the minimal inhibitory concentration.[7–9] Most published data on the conservative management of CRBSI relate to CoNS infection.[5,10,11] Daptomycin (DPT) in particular is a lipopeptide antibiotic which offers great potential due to its activity on bacterial biofilm, which consists of multilayered cell clusters embedded in a matrix of extracellular polysaccharide (slime), facilitating adherence of microorganisms to surfaces, and reducing the efficacy of the host's immune system and of anti-microbial therapy.[12] Indeed, it rapidly penetrates the biofilm and, in contrast with other molecules, in vitro data show that its bactericidal activity does not require cell division or cell metabolism, probably as a consequence of its direct action on the bacterial membrane.[13]

We previously showed that a short course of DPT lock and systemic therapy allows good rates of catheter salvage in case of CRBSI due to CoNS.[14] However, as the few existing in vivo studies on DPT as ALT, including ours, showed success rates between 75% and 85%, further strategies are needed in order to improve rates of catheter salvage.[14–16]

Among molecules used as ALT, interest is growing about the use of Taurolidine, a molecule offering unique antiseptic and anti-thrombotic characteristics.[17–19] It is a non-toxic agent with a wide spectrum of activity against gram-positive and gram-negative bacteria, and against fungi.[20,21]

While there is an abundance of data concerning its use in catheter infection and thrombosis prophylaxis in cancer and non-cancer patients, little is known of its role for the treatment of CRBSI. Two studies have showed its efficacy in treating CRSBI in cancer patients.[22,23]

In order to improve management of CRBSI in our regional clinical settings, we introduced local protocols which, in case of CRBSI due to CoNS, consist in instilling DPT as ALT and systemic treatment, followed by Taurolidine as ALT, together with systemic antibiotic therapy in order to achieve 14 days of treatment.

We aimed to assess the efficacy of such guidelines for the conservative management of long-term in-dwelling catheters.

Materials and methods

Study design and participants

We retrospectively included patients hospitalized for CRBSI due to CoNS and who received DPT and Taurolidine as ALT. As most data on lock therapy focus on totally implanted venous access devices (TIVAD), only patients with TIVAD CRBSI were included in the analysis. Three clinical institutions in our geographical area participated in this study: Cannes General Hospital, Antibes General Hospital and Institut Polyclinique d'Oxford (IPOCA). Data were extracted from the institutions' electronic databases, files were reviewed in order to confirm the diagnosis and physicians who had been directly involved in the care of these patients took part in this analysis.

The study was submitted to the Health Data Hub (https://www.health-data-hub.fr/depot) and all patients provided written informed consent.

CRBSI were defined according to current guidelines,[5] while susceptibility testing of the isolates was performed with automated methods. EUCAST breakpoints were used for interpreting minimal inhibitory concentrations.

Background parameters and information on duration of ALT, type, and duration of systemic therapy and outcome were collected for each subject.

Local protocols for the conservative management of CRBSI

In case of CRSBI due to CoNS, local protocols for conservative management of catheter consist in instilling DPT, diluted in Ringer's solution (5 mg/ml). Five milliliters[24] of the prepared, heparin-free solution (i.e. 25 mg of DPT) are instilled in the catheter lumen for 18 h daily, during three consecutive days.[25] ALT is initially combined with systemic treatment, *i.e.* DPT (using the remaining quantity from the same vial) with Rifampin, due to their synergistic activity.[11] Treatment may then be modified, commonly after 3–4 days, in order to achieve the recommended duration of systemic treatment of 10–14 days.[5] The choice of antibiotics for the switch is guided by microbiological results and susceptibility testing and is preferentially administered orally. Rifampin is generally discontinued concomitantly with DPT, as its administration is mainly justified by its synergistic activity with DPT on the biofilm. Infusions can generally be resumed immediately following the 3 days of ALT.

After 3 days of DPT as ALT, Taurolidine lock is introduced from day 4 to day 14 and administered together with antibiotic therapy. According to the manufacturer's recommendations and to the volume of the device,[26] 5 ml of Taurolidine citrate are instilled daily (0.3 ml/s) and maintained for at least 2 h. Infusions in the device are not administered during the 2 h of Taurolidine lock but are allowed during the rest of the day.

Patient follow-up

Clinical response was defined as complete resolution of clinical signs and symptoms of infection after ALT initiation, while retention of the TIVAD 1 month after discontinuing antibiotic therapy was considered clinical success.

Catheter retrievals within 30 days of ending antibiotic therapy were considered as failures, with the exception of device removals resulting from their being no longer necessary.

Failures were divided into those with microbiological documentation of CRBSI relapse and those with recurrence of fever of unknown origin as the reason for such a removal.

In case of death within 30 days following the end of the antibiotic course, patients were excluded but causes of death were analyzed in order to confirm that they were unrelated to infection.

Results

Population characteristics

From April 2018 to September 2021, 22 subjects who received ALT for a TIVAD CRBSI due to CoNS infection were extracted from the databases of the three clinical institutions.

Their main characteristics are summarized in Table 1. Their mean age was 64 years and the majority had been diagnosed with a solid tumor and had ongoing parenteral nutrition.

In 9 out of 22 cases a short course of empirical antibiotic treatment had been prescribed before ALT. No patients had received previous ALT.

For all subjects fever was present at their admission and diagnosis of CRBSI was confirmed by a differential time of positivity of at least 2 h between blood cultures drawn from the catheter and the peripheral vein.

Staphylococcus epidermidis was the most frequently identified CoNS found responsible for CRBSI, followed by *Staphylococcus haemolyticus*, while two subjects had a polymicrobial infection with two strains of CoNS (Table 1).

Table 1. Characteristics of patients included and clinical outcome ($n = 22$).

Age in years, mean [SD]	64 [10.9]
Gender (male), no. (%)	13 (59)
Underlying disease	
Metastatic solid neoplasia, *n* (%)	12 (54)
Solid neoplasia without metastasis, *n* (%)	7 (32)
Hematological cancer, *n* (%)	2 (9)
Other	1 (5)
Performance status, mean (IQR)	1.7 (1.4)
Ongoing parenteral nutrition, *n* (%)	14 (64)
Previous episode of CLABSI, *n* (%)	1 (5)
Characteristics of the catheter	
Port-a-cath, *n* (%)	22 (100)
Catheter life span in months until infection episode, mean (IQR)	9.6 (24.8)
Microorganisms	
Staphylococcus epidermidis, n (%)	18 (82)
Staphylococcus haemolyticus, n (%)	2 (9)
Polymicrobial, *n* (%)	2 (9)
Treatment	
DPT ALT mean [SD] duration (days)	3 [0]
Mean [SD] DPT dose received (mg/kg)	7.5 [1.0]
IV DPT mean [SD] duration (days)	3.9 [3.6]
Mean Rifampin [SD] dose received (mg/kg)	19.5 [3.5]
IV Rifampin mean [SD] duration (days)	3.0 [0.2]
Total mean [SD] duration of antibiotic treatment	13.5 [2.8]
Mean [SD] Taurolodine ALT duration (days)	10.5 [1.2]
Antibiotic used for the switch from DPT and Rifampin, *n* (%)	
Linezolid	17 (77)
Tedizolid	2 (9)
Other	3 (14)
Outcome	
Clinical success, *n* (%)	21 (95)
Clinical failure, *n* (%)	1 (5)

Patient outcomes

All patients received 25 mg/day of DPT ALT for 3 days according to our local guidelines. After receiving systemic DPT (7.6 mg/kg/day) and Rifampin (19.5 mg/kg/day) for a mean period of 3.9 and 3.0 days, respectively, the majority of patients were switched to oral treatment in order to complete the 14 days scheduled total treatment duration. Linezolid was the most frequently prescribed compound (Table 1). Concomitantly to this switch, 5 ml/day of Taurolidine were instilled in the catheter hub in all patients but one, for a mean duration of 10.5 days (Table 1). One subject did not undergo ALT, as she did not respond to initial antibiotic treatment and blood cultures drawn following 3 days of DPT confirmed the same, previously isolated, CoNS. This was the only unfavorable outcome. The other 21 subjects responded to treatment, tolerated systemic and ALT therapies well, fever rapidly disappeared and they all retained the device 1 month after completing their antibiotic course. Infusions via catheter devices were continued for all subjects, either daily in case of parenteral nutrition or analgesic therapy, or intermittently in case of chemotherapy. Clinical success was therefore obtained for 21 out of 22 subjects (95%, Table 1).

Discussion

A short-course parenteral treatment with DPT, followed by a switch to oral antibiotics and Taurolidine ALT in patients with CoNS CRBSI allowed high rates of catheter salvage.

Rates of success are particularly encouraging considering the prevalence of comorbid conditions in such patients, most of whom had advanced cancer.

The efficacy of DPT against in vitro biofilm-forming strains of Staphylococci has been shown in several studies. Indeed, Raad et al.[27] found that it acts faster than most

other compounds against central venous catheter biofilm infections, while Edmiston et al.[28] showed that DPT, Rifampin, and Linezolid had greater efficacy and speed in eradicating microbial adherence of staphylococcal isolates compared to Vancomycin or Ceftriaxone in an antibiotic lock model. The choice of associating DPT and Rifampin could be explained by the synergistic action of such molecules, DPT opening channels in the cell membrane for hydrophobic molecules such as Rifampin.[12]

To our knowledge, this is the third study to demonstrate the efficacy of Taurolidine as ALT for treating infected catheters, in combination with systemic antibiotic treatment. Indeed, data regarding Taurolodine use in therapeutic protocols are scarce. Haag et al.[22] report 67% efficacy when a short-course of Taurolidine was associated with antibiotic treatment in cancer patients with long-term CRBSI, most of which were CoNS-related infections. Morevoer, Brescia et al.[23] in a retrospective analysis found high rates of success with 2% Taurolidine lock 5 days plus systemic antibiotic treatment in cancer patients with TIVAC CRSBI.

Although the retrospective character of our study and its design require prudent conclusions, we found that its association with DPT offers very high success rates. Indeed, in patients with similar characteristics of severe cancer, we found that DPT ALT alone allowed success rates of 76%,[14] while its association with Taurolodine here allowed a clinical success in 95% of cases.

However, the optimal duration of Taurolidine and the best combination with antibiotic treatment are still unknown. We suggest that in vitro studies could be helpful to assess Taurolidine's synergistic properties with antimicrobials on the bacterial biofilm and to determine which would be the best combination of molecules for in vivo trials. Moreover, prospective studies are needed in order to compare strategies with antibiotic therapy alone and with combinations of Taurolidine and antibacterial compounds. Besides, it would be interesting to compare strategies like ours combining Taurolodine and DPT with locks with only Taurolodine, as showed by Brescia et al.[23] Potential advantages of associating such molecules could be the increased ability to penetrate the biofilm and to shorten treatment courses by combining a potent antimicrobial compound with a molecule with antiseptic and anti-thrombotic properties. Disadvantages could come from increased costs, although the price of DPT dramatically reduced since its recent conversion from brand to generic compound.

The limitations of the study include, as previously cited, its retrospective character and the small number of participants. Larger prospective studies are needed before generalizing the use of ALT for the conservative management of CRBSI. Moreover, the study design cannot definitely conclude whether the combination of ALT and systemic treatment allows better success rates than systemic treatment alone. However, previous data on CRBSI show that, without local instillation in the lumen, *in situ* antibiotic concentrations are often insufficient to achieve effective penetration within the biofilm.[7] Besides, we think that despite its retrospective character, the risks of bias by a pre-selection of patients are low, as such guidelines for ALT were applied for all subjects filling the criteria for a conservative management of CoNS CRBSI.

In conclusion, a 3-day course of ALT and systemic DPT, followed by a short course of Taurolidine ALT and oral antibiotic treatment, were associated with high rates of catheter salvage in case of CoNS-associated CRBSI. Further prospective studies could support our findings.

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Author contributions

Conceived, designed the study, and collected data: M.V., E.D., and P.F. Analyzed the data: M.V. Wrote the manuscript: M.V. Edited the manuscript: S.M., L.L., and A.S.

Data availability statement

All available data have been included in the manuscript

Declaration of conflicting interests

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Institutional review board statement

This was a retrospective study, submitted to the Health Data Hub (https://www.health-data-hub.fr/depot). According to French laws, no etic committee approval is necessary.

Informed consent statement

Patients received written information of this study and gave their consent to the retrospective collection of their data.

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