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REVIEW

Antimicrobial lock therapy in central-line associated bloodstream infections: a systematic review

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Abstract
Purpose Antimicrobial lock therapy (ALT) seems a promising approach for treatment of central line associated bloodstream infections (CLABSI). The recent introduction of molecules such as daptomycin and tigecycline, alone or in combination with other molecules, improved chances of efficacy of ALT, due to their activity on the bacterial biofilm. Our aim was to review the literature concerning ALT for CLABSI, including data concerning novel molecules.
Methods We included case-control studies evaluating two or more molecules as ALT in central venous catheter infections extracted from the Medline database. Among 221 available articles in Pubmed, 54 were selected for their particular interest concerning ALT.
Results Incidence of CLABSI is high worldwide. Mechanisms of catheter infection include contamination by skin bacteria, hand contamination and hematogenous diffusion. Catheter-infection is associated with biofilm formation, which reduces the efficacy of ALT. The most promising situation for ALT to succeed in salvaging a catheter appears to be coagulase-negative Staphylococcus infection, which is the main causative agent of CLABSI. Daptomycin, Tigecycline, Ethanol and Taurolidine appear as the best options for treating CLABSI; data are mostly available for Daptomycin, which showed, alone or associated with Rifampin, good in vitro potency on biofilm, but few in vivo data exist on efficacy.
Conclusions The introduction of novel molecules has increased chances of catheter salvage with ALT in case of CLABSI, but further in vivo studies are needed.

Keywords Central-line associated bloodstream infections · Antimicrobial lock therapy · Biofilm · Catheter salvage

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Introduction

Central-line related bloodstream infections (CLABSI) are associated with increased morbidity, mortality and costs [1].

Antibiotic failure to treat CLABSI is essentially linked to microbial biofilms, which develop when microorganisms irreversibly adhere to the catheter surface and produce extracellular polymers that facilitate adhesion and provide a structural matrix. This matrix acts as a filter and potentially reduces antibiotic capacity to inhibit microorganisms [2].

In the majority of cases, catheter removal is considered the best option to cure patients [3].

However, catheter salvage could be an option especially for situations where venous access is poor and incidence of infection is high, such as onco-hematological and hemodialysis patients, as well as for subjects receiving parenteral nutrition [4, 5].

While for *Staphylococcus aureus* and fungi infections catheter removal is generally considered the best strategy, conservative treatment remains more controversial in case of CLABSI due to other agents, such as coagulase-negative staphylococci (CoNS) and gram-negative bacilli (GNB) [3, 4].

Table 1 Current knowledge on available molecules for antimicrobial lock therapy

Molecule used as antimicrobial lock therapy (ALT)	Main articles
Aminoglycosides could be active against *S. aureus* and coagulase-negative staphylococci (CoNS) in lock solutions, but data concerning their efficacy for inhibiting biofilm-forming colonies are contradictory. Activity of amikacin could be promising for treating non-seriously ill patients with Gram-negative bacilli CLABSI, although further studies are needed. Possibly toxic systemic concentrations when gentamycin administered as ALT	Bookstaver, Fernandez-Hidalgo, Funalleras, Dogra
Antifungals azole agents have poor activity against Candida sp. biofilm forming colonies, while lipid Amphotericin B formulations display better success rate. However, current guidelines recommend catheter removal in case of fungal infection	Walraven, Raad
Vancomycin could be effective against gram-positive catheter-related bloodstream infections (CLABSI), especially for CoNS. It could be associated with heparin to increase its bactericidal capacity. Generally prescribed with systemic treatment. Timing of lock still to be determined	O'Horo, LaPlante, Bookstaver
Daptomycin strong capacity to inhibit replication of gram-positive biofilm-forming bacteria. It could be associated with Ringer's solution to prolong its activity after the end of treatment. Same capacity to inhibit biofilm-forming CoNS and *S. aureus* strains. Probably superior to vancomycin as ALT for inhibiting bacterial growth, equally for CoNS and *S. aureus*. Synergistic with rifampin, even for stationary phase bacteria. In vivo studies very rare, duration and modality of ALT remain undetermined	Van Praagh, Aumeran, Estes, Dominguez-Herrera, LaPlante, Cirioni, Del Pozo
Tigecycline good potential as ALT, but few studies at present. Probably superior to Vancomycin, but inferior to Daptomycin, for gram-positive bacteria. It offers a wider spectrum of activity compared to vancomycin and daptomycin, including also some potential for treating Gram negative bacilli-CLABSI, but data are lacking. Like daptomycin, it is synergistic with rifampin	Aybar, Raad
Ethanol few studies available, but extremely effective to inhibit bacterial growth as ALT. At least as powerful as daptomycin. Requires caution regarding side effects (catheter integrity)	Passerini de Rossi, Abu-el-Hajia
Taurolidine antiseptic drug with potential capacity to reduce biofilm formation. However, comparative studies with molecules other than heparin are needed before generalizing its use in the management of CLABSI	Handrup

Antimicrobial lock therapy (ALT) in particular appears as a promising treatment strategy for conservative management of the catheter. It consists in instilling an antibiotic solution into the hub of the central venous catheter when it is not in use, to achieve a concentration of the antibiotic that is many-fold higher than the minimal inhibitory concentration (MIC) for the bacteria involved [6, 7]. The antibiotic should remain for a specified duration, typically between 18 and 24 h and this strategy appears particularly useful for patients in whom reintroducing a catheter may be difficult [6].

Besides, novel molecules such as Daptomycin and Tigecycline have demonstrated potential efficacy, alone or in combination with other molecules, due to their mode of action on bacterial biofilms.

However, making evidence-based decisions regarding ALT recommendations is sometimes difficult [8–10] and protocols are usually developed on the basis of local experience.

Our aim was to review the literature concerning ALT for CLABSI, including data on novel molecules, which have added extra potential to ALT strategies.

Methods

We obtained relevant articles from the Pubmed database, using the broad search terms "central line infection" and "lock therapy". Case–control studies evaluating two or more drugs as ALT in central venous catheter infections were included regardless of date, language and publication status. Experimental models and in vivo studies on humans or animals were considered.

The Pubmed search was performed in April 2014 and updated in December 2014. Among 221 articles selected in Pubmed, 217 contained an abstract, 204 were written in English and 103 focused more specifically on the research theme. Among these 103 papers, 54 were retained for their particular interest concerning ALT. Publication dates of selected articles ranged from 1990 to 2014. The remaining articles were excluded as their content did not provide further information with regard to the selected papers or were not considered relevant. Tables 1 and 2 resume main results of this research.

Results

Incidence of CLABSI and clinical outcome

In the United States, approximately 80,000 cases of CLABSI occur among 3 million central venous catheters (2.7 %) [5]. The same problem is encountered in Europe, where the incidence of health-care associated infection, which includes CLABSI, reaches 10.1 % [11].

A recent CDC report revealed encouraging data, with a 58 % reduction of CLABSI in ICUs from 2001 to 2009.

Table 2 Antimicrobial lock therapy (ALT) according to pathogen

Pathogen	Antimicrobials available as ALT and lock protocol	Comments
Coagulase-negative Staphylococci (CoNS)	Vancomycin 1–5 mg/ml, added to heparin 2,500–5,000 IU/ml, lock for 12 h/day	Optimal duration of lock unknown, typically 5 ml of solution in implanted ports
	Daptomycin 5 mg/ml, diluted in lactated Ringer's solution. Duration of lock from 12 to 18 h/day	Heparin unnecessary, but some authors add 100 IU/ml for implanted ports, 5,000 IU/ml for hemodialysis catheters. Daptomycin is synergistic with rifampin. Duration of lock in clinical studies is 14 days. Typically 5 ml of lock solution in ports.
	Tigecycline, 2 mg/ml	Synergistic with rifampin. In vivo studies lacking
	Linezolid 2 mg/ml	Synergistic with N-acetyl-cysteine. Studies only in vitro or in animals
	74 % Ethanol 3 ml, combined with 1 ml 0.9 % NaCl. Lock 20–24 h/day	Duration of lock 3 days. Risk of device structural changes, especially if polyurethane catheters. Possible addition of enoxaparin sodium 400 IU/ml, but some authors raise doubts about compatibility with ethanol
	Taurolidine 2.5 ml, either combined with 4 % sodium citrate, sodium heparin 2,500 IU or with 25,000 IU urokinase	
	Gentamicin 5 mg/ml plus tetrasodium EDTA 30 mg/ml for 1 day, in association with systemic Vancomycin	Some doubts raised about potential systemic ototoxicity of gentamicin ALT. Data concerning capacity to inhibit biofilm are contradictory
Staphylococcus aureus		Catheter removal suggested
	Vancomycin, 1–5 mg/ml, heparin unnecessary	
	Daptomycin 2.5 mg/ml, diluted in lactated Ringer's solution	Synergistic with rifampin
	Tigecycline 2 mg/ml	Equivalent activity to vancomycin
	Linezolid 2 mg/ml	
	Taurolidine, same concentrations as for CoNS	
	Gentamicin 5 mg/ml plus EDTA 30 mg/ml, for 3–5 days, in addition to systemic vancomycin	Same potential risks of toxicity than those described for gentamicin for treating CoNS CLABSI
Gram negative bacilli	Ciprofloxacin or amikacin, both at the dose of 2 g/L, plus heparin 20 IU/ml	2 ml of lock solution if tunneled catheter; 3–5 ml if implanted ports
	Taurolidine, same concentrations as for CoNS	
	Tigecycline, no data on dosing	
	Gentamicin 5 mg/ml plus EDTA 30 mg/ml for 3 days, combined with systemic Gentamycin	Risk of otoxicity. Studies only in animals
Fungi		Catheter removal suggested
	Liposomal Amphotericin B 1 mg/ml	
	Amphotericin B lípid complex (ABLC) 2 mg/ml, plus EDTA 30 mg/ml	Duration of antifungal lock varies between 6 and 24 h/day
	Caspofungin 2 mg/liter	The combination of ABLC and EDTA is the most effective against *Candida* biofilms
	Ethanol 25–60 %	

Indeed, Fagan et al. [12] measured incidence trends in pathogen-specific CLABSI in US ICUs from 1990 to 2010, showing a decline since 2006, with the exception of infections due to *S. aureus* in pediatric ICUs, probably as a consequence of surveillance programs [13].

Dreesen et al. [14] evaluated differences between cancer patients and those with other conditions. Indeed, they found that in patients with a benign underlying disease, rates of CLABSI range between 0.19 and 2.441 episodes for 1,000 catheter-days, with a median of 0.82 episodes for 1,000 catheter-days. This rate increases in studies including over 50 % cancer patients, where the incidence rate of CLABSI lies between 1.9 and 6.8 episodes per 1,000 catheter-days, with a median of 2.71 [14].

According to a recent systematic review and meta-analysis, the odds ratio for in-hospital death due to CLABSI was 2.75 [CI 1.86–4.07], decreasing to 1.51 [CI 1.02–2.65] when patients were matched using an illness severity index [1].

Mechanisms for CLABSI

Endogenous microorganisms residing on the skin or in the catheter hub are the main cause of CLABSI. In this case leading pathogens are *S. aureus* and CoNS [3, 11, 15].

Other sources of CLABSI are organisms spread by contaminated hands or intravenous fluids, or hematogenous diffusion. In these cases, involved microorganisms are more heterogeneous, including *Enterobacteriaceae*, *Pseudomonas* and fungi [15].

Moreover, the ability of a microorganism to attach to catheters depends on the properties of the catheter surface, the microorganism itself and the host. In the first case, physical irregularities on the catheter can increase risks of adherence. Among risk factors linked to the microorganism, binding characteristics of infective agents differ, in particular their capacity to link to fibronectin and fibrinogen. Besides, bacteria can produce extracellular polymeric products, contributing to the development of the biofilm, which reduces antibiotic capacity to cure catheter infection [14].

Indeed, the biofilm is formed by bacteria in stationary phase embedded in an extracellular matrix; consequently, it protects bacteria against both the immune system and antimicrobial agents and could be responsible for recurrent bacteremia [16–20].

Moreover, Mekhni et al. [21] found that strains of *Staphylococcus epidermidis* isolated from CLABSI produce more biofilm than strains from non catheter-related bacteremia and those considered as commensal isolates.

Among risk factors for CLABSI linked to the host, age, co-morbid conditions, severe immunodepression and the individual capacity to produce fibronectin and fibrinogen are those most often stated.

Several studies describe potential risk factors for CLABSI. Dreesen et al. [14], focusing on patients receiving home parenteral nutrition, listed factors that were device-related, e.g., catheter caliber, education-related, e.g., lack of training with provision of detailed information to patients, patient-related, e.g., age and regular smoking and therapy-related, e.g., duration of parenteral nutrition and days of administration,

Studies of antimicrobials used for ALT

Aminoglycosides

In an animal study, Chauan et al. [22] showed that gentamicin-EDTA lock therapy is active against *S. aureus* and CoNS biofilms. Fortun et al. used this compound as ALT for 14 days, in association with systemic treatment, for gram-negative rod CLABSI.

Gentamicin ALT is typically administered at 2.5 or 5 mg/ml concentrations [23]. However, data about its efficacy are contradictory, as Lee et al. [24] showed that it was not effective over 5 days of ALT in in vitro biofilm models, nor were cefazolin, nafcillin or erythromycin, while Fernandez-Hidalgo et al. [25] found that gentamicin ALT was generally effective on *S. aureus* biofilms in rabbit catheters.

Amikacin is generally administered 12 h/day at the dose of 3 mg for a period varying from 14 to 27 days and is generally associated with systemic treatment [26].

Bestul et al. [15] reported a trial on 11 patients receiving home parenteral nutrition, where 2 ml/day of 1.5 mg/ml amikacin, locked for 12 h, resulted in 90 % successful treatment of CLABSI.

Antifungal lock therapy

Candida species are associated with the highest overall crude mortality due to bloodstream infection, comparable to that of Pseudomonas. *Candida albicans* is the most common fungal species responsible for CLABSI (see Table 2).

Although guidelines recommend catheter removal in case of CLABSI due to fungi [3, 27], there are reports of effective ALT.

If azoles generally have poor activity against Candida biofilms, lipid Amphotericin formulations, echinocandins and 25 % ethanol showed good success rates in salvage therapy of CLABSI [28]. Indeed, Ramage et al. [29] showed that liposomal Amphotericin B displays rapid dose-dependent activity against *C. albicans* biofilm. Raad et al. [30] compared EDTA, Amphotericin B lipid complex (ABLC) and EDTA plus ABLC against *C. albicans* and

Candida parapsilosis, showing that EDTA plus ABLC was the most effective against biofilms.

Treatment is generally administered for 14 days, in conjunction with systemic antifungal therapy.

In case of polyurethane catheters, ethanol solutions cannot be used because of potential incompatibility [28].

Vancomycin lock therapy

Vancomycin is a glycopeptide that is active against gram-positive bacteria, including methicillin-resistant staphylocci. The antibiotic is prescribed as ALT using concentrations ranging from 1 to 5 mg/ml. Duration of locks varies from 3 to 27 days and ALT is generally associated with systemic treatment [6]. Indeed, Bookstaver et al. [23] showed that active systemic therapy, associated with vancomycin ALT, alone or together with gentamicin or ethanol, allowed good success rates while avoiding catheter removal.

Beigi et al. [31] compared a strategy with vancomycin lock and systemic ceftriaxone with a combination of systemic vancomycin and amikacin, finding that the ALT arm was superior for fever resolution and catheter retention. Vancomycin ALT was administered at the dose of 500 mg and injected in the lumen every 48 h for 7 days.

Interestingly, LaPlante et al. [19] showed that the addition of heparin to vancomycin enhanced the activity against biofilm-forming *S. epidermidis*, but not biofilm-forming *S. aureus.*

Daptomycin lock therapy

Daptomycin (DPT) is a cyclic lipopeptide antibiotic, which has a rapid, concentration-dependent bactericidal activity against most clinically important gram-positive bacteria, including methicillin-resistant *Stahylococcus aureus* (MRSA), CoNS, vancomycin-resistant enterocci and penicillin-resistant *Streptococcus pneumoniae*. Moreover, its in vitro capacity to destroy staphylococcal biofilm offers interesting potentialities for the treatment of CLABSI.

DPT is a calcium-dependent antibacterial agent, working optimally in vitro with levels of free calcium ions at physiological concentrations (50 μg/ml). Most studies are, therefore, conducted using DPT with lactated Ringer's solutions (containing 50–80 μg/ml of calcium) [18, 32].

Estes et al. [33] compared four strategies for eradicating biofilm-producing strains of MRSA embedded on silicon disks, including DPT or minocycline, both alone or associated with 25 % ethanol. Authors found that 5 days of 4-h daily exposures to DPT (2.5 mg/ml), independently from ethanol use, and minocycline associated with ethanol were superior to minocycline alone for reducing MRSA colony counts.

Aumeran et al. [18] compared the effectiveness of vancomycin (5 mg/ml), DPT (5 mg/ml) and 40 % ethanol (with enoxaparin sodium 400 IU/ml) lock solutions in destroying a pre-established biofilm of *S. epidermidis.* Authors found that mean logarithmic reductions in bacterial growth were statistically greater for DPT and ethanol than for vancomycin, while bacterial reformation after 24 h of exposure to ALT was higher for vancomycin and DPT than for ethanol.

Van Praagh et al. [32] compared the efficacy of vancomycin and DPT ALT in a rat model of Staphylococcal central venous catheter biofilm. DPT and vancomycin were administered as ALT at concentrations of 5 mg/ml 18 h daily for 3 days in rats with central venous catheter infection caused by methicillin-resistant *S. epidermidis* (MRSE) strains susceptible to both molecules (MIC 1 μg/mL for DPT and 2 μg/mL for vancomycin). Animals were also administered the same antibiotics subcutaneously: DPT at the concentration of 40 mg/ml once daily and vancomycin 50 mg/kg twice daily. DPT and vancomycin both caused rapid elimination of MRSE from central venous catheters and although differences were not statistically significant, DPT appeared to act slightly faster. However, authors combined systemic treatment with ALT and no port-catheter was included in the experiment.

Interestingly, authors found no difference in bacterial inhibition during ALT when DPT was diluted with either Ringer's or saline solutions, while dilution with Ringer's was superior in sustaining bacterial clearance 7 days after the last ALT.

Dominguez-Herrera [34] also compared DPT with vancomycin against biofilm-producing MRSE in an experimental in vivo model, showing that DPT reduced bacterial concentrations in the catheter by a factor of 3 log10 CFU/mL compared to vancomycin.

Moreover, LaPlante et al. [19] compared in vitro activity of DPT and vancomycin lock solutions on staphylococcal biofilm in a central venous catheter model, showing that after 72 h of exposure (with each compound at a concentration of 5 mg/ml), they displayed equivalent capacity to eradicate *S. epidermidis* growth, while DPT was superior to vancomycin for inhibition of *S. aureus*. Authors also showed that adding heparin to DPT is not necessary to eradicate *S. epidermidis* or *S. aureus*, differing from vancomycin.

Meije et al. [35] showed that DPT achieved greater activity than vancomycin against biofilm-forming methicillin-susceptible *S. aureus* and MRSA, but concentrations of 50 mg/ml performed better than the usual dose of 5 mg/ml.

The combination of DPT with rifampin appears useful for treating biofilm, as a consequence of a synergistic mechanism, as showed by Cirioni et al. [36] Indeed, authors found that the combination of these molecules had higher efficacy than that of each single compound for treating a

rat model of Staphylococcal infection. Authors suggest that the positive interaction between DPT and rifampin could be explained by the mechanism of action of DPT, which opens channels in the cell membrane, promoting entry of hydrophobic drugs such as rifampin.

In vivo studies on humans concerning ALT with DPT are rare. In a short series of 13 patients, Del Pozo [37] showed that DPT lock therapy is effective in CLABSI due to CoNS infection. In this study, 5-milliliter syringes were filled with DPT (5 mg/ml) plus heparin and reconstituted in Ringer's lactate solution. The antimicrobial locks were replaced daily, for a mean duration of 14 days, associated with systemic treatment in 85 % of cases. Success was defined as fever resolution, negative blood cultures and catheter salvage within one month after the end of treatment, and was achieved for 11 out of 13 subjects. The catheter had to be removed during therapy in two patients, due to persistent fever.

In another short case series, Tatarelli et al. [38] describe eight patients with CLABSI mainly due to CoNS infection and with previous failure to vancomycin and cefazolin, where six of them were successfully treated with DPT as systemic and lock therapy. Mean duration of ALT was 13 days.

In vivo studies using ALT with DPT require the use of Ringer's lactate solution (60–130 mg/l calcium bicarbonate) to approximate calcium concentrations used in the majority of in vitro studies [19].

Tigecycline lock therapy

Tigecycline, a derivative of tetracycline, acts against strains producing biofilms and has a wide spectrum of action, including the majority of gram positive and gram negative bacteria.

However, there are few data concerning its use in ALT.

In CoNS-infected polyurethane catheters inserted in rabbits, electron microscopy showed that Tigecycline was superior to vancomycin in reducing bacterial growth [39].

Raad et al. [17] compared the activity of various compounds against MRSA embedded in biofilm, showing that after 3 days of 4-h daily exposures, Tigecycline ALT was faster than Linezolid, Rifampin and Vancomycin in eradicating MRSA from biofilm, but slower than DPT. Furthermore, the addition of Rifampin to Tigecycline or DPT enhanced antimicrobial activity against MRSA.

Ethanol lock therapy

In vitro studies concerning ethanol, EDTA and levofloxacin lock therapy showed that ethanol, alone or combined with EDTA, was effective as lock therapy against *Strenotrophomonas maltophilia* CLABSI [40].

Moreover, Aumeran et al. [18] showed that ethanol and DPT were more effective than vancocymin for treating *S. epidermidis* biofilms.

The New York Presbyterian Hospital guidelines suggest treating catheters with 3 ml of 74 %ethanol combined with 1 ml of NaCl 0.9 %, preceded and followed by washing with NaCl, and to avoid ethanol use in case of polyurethane catheters [41]. Similarly, Dannenberg et al. [42] suggest injecting 2.3 ml 74 %ethanol and to lock for 20–24 h/day for 3 days. However, Abu-El-Haija et al. [43] found that ethanol ALT decreased the incidence of CLABSI but had a negative impact on line integrity, suggesting careful selection of patients for ethanol therapy. Similarly, a recent systemic review of ethanol ALT [44] by Mermel and Alang showed high rates of systemic side effects and device's structural changes, especially for polyurethane catheters.

Linezolid lock therapy

Very few data are available concerning the potential role of linezolid as ALT.

Fernandez-Hidalgo et al. [25] showed that linezolid and vancomycin had equivalent activity on MSSA and MRSA strains responsible for catheter-related infections in a rabbit model.

Moreover, Leite et al. [45] reported a synergistic effect of linezolid and N-acetyl-cysteine for treating *S. epidermidis* biofilms.

Telavancin lock therapy

Telavancin is another antibiotic with some potential in ALT. However, to our knowledge, no consistent data have been published at present regarding its efficacy. LaPlante et al. [46] showed that Telavancin 2 5 and 5 mg/ml were physically compatible with heparin 2,500 units/ml and citrate 2.2 and 4 % over 72 h for lock solutions.

Taurolidine

Taurolidine is a drug with antimicrobial and anti-lipopolysaccharide properties, which has demonstrated its capacity to inhibit in vitro biofilm formation [47].

It is derived from the amino-acid taurine and acts via the release of three active methylol groups, which react with the bacterial cell wall, resulting in bacterial lysis and bacterial endotoxin neutralization [48].

Comparing the effect of taurolidine and heparin in biofilm formations, Handrup et al. [47] showed that taurolidine was more effective in preventing CLABSI.

These results are confirmed by Shah et al. [49], who showed that ALT with taurolidine was superior to heparin

for bactericidal activity against several bacteria responsible for catheter infections.

However, comparative studies with other molecules are lacking; therefore, strategies for its use are at present based on local experience rather than on guidelines [7].

Studies evaluating ALT and systemic therapy for CLABSI

O'Horo et al. [6] analyzed studies which compared ALT to systemic therapy, finding that the combination of both was superior (OR 0.2, 95 % CI: 0.10–0.39) to systemic antibiotic alone for catheter salvage, with 10 % of locked patients requiring replacement, compared to 33 % of subjects without lock.

Bookstaver et al. [23] evaluated clinical outcomes with ALT as adjunctive treatment to systemic therapy in case of CLABSI, in a small series of patients. The main pathogens were CoNS (35 %), MRSA (23 %) and GNB (23 %), while the main drugs used for ALT were DPT, vancomycin and gentamicin. Mean duration of ALT was 8.9 days. Authors found that blood culture sterilization was obtained in 69 % of cases and catheter salvage in 42 % of cases. Moreover, longer ALT duration (>9 days) was correlated with achieving catheter sterilization with an OR of 1.367 for each day above the mean.

ALT in hemodialysis-related CLABSI

As hemodialysis catheters have certain specificities regarding type of device and patient characteristics, ALT in this context was analyzed separately.

A systematic review and meta-analyis on hemodialysis-related CLABSI recently revealed that ALT and guidewire exchange had similar rates of success and both were superior to systemic therapy alone. The highest cure proportion was reached for CoNS infection, followed by GNB and *S. aureus*. In case of *S. aureus* infection, guidewire exchange was superior to either systemic therapy or ALT [50].

Joshi et al. [51] prospectively examined the efficacy of systemic and ALT antibiotics for the treatment of tunneled hemodialysis CLABSI, showing that ALT was effective in 59 % of cases, with similar success rates in gram-positive and gram-negative infections (63 vs 62 %, respectively).

Lee et al. [24] studied different combinations of ALT in adult hemodialysis patients. Locks included vancomycin, imipenem, ciprofloxacin and ceftazidime and were instilled into the lumens of catheters on completion of each dialysis session and withdrawn immediately prior to the next session. Authors found that ALT combined with systemic treatment was superior to systemic therapy alone.

Moreover, Saxena et al. [52] showed that a cefotaxime-heparin lock was effective for preventing CLABSI in *Staphylococcus aureus* nasal carriers undergoing hemodialysis through tunnelled, cuffed catheters, with the exception of MRSA carriage.

Citrate has been used clinically as an anticoagulant in heparin-free catheter locks and a systematic review and meta-analysis performed by Zhao et al. [10] showed that antimicrobials associated with citrate locks in hemodialysis patients could reduce the incidence of CLABSI, whereas citrate alone was not superior to heparin. Interestingly, glyceryl trinitrate seems synergistic with citrate and this combination appears attractive as a lock solution [53].

In an observational, non-comparative, prospective cohort study on patients with GNB-CLABSI, where the majority of devices were hemodyalisis catheters, Funalleras et al. [4] showed high rates of success using ALT with ciprofloxacin or amikacin, both at 2,000 mg/L and mixed with sodium heparin (20 UI/ml). Total volume of ALT solutions depended on the type of device, usually 2 mL for tunneled catheters and 3–5 mL for implanted ports. Median days of ALT were 13, associated with systemic treatment for a median period of 15 days.

Few studies have focused on the potential side effects of aminoglycosides as ALT: Dogra et al. [54] recently showed that plasmatic concentrations of gentamicin when used as ALT for the prevention of hemodyalisis-related CLABSI could be associated with ototoxicity.

Discussion

Studies evaluating ALT for central venous catheter infections vary according to the type of antibiotic and concentrations used. Many catheter-associated infections are related to intraluminal biofilms and are often difficult to treat. The recent introduction of novel molecules has added potentialities for improving their treatment, but studies on ALT, alone or associated with systemic antimicrobials, are often limited by the small number of patients included or by the study design.

Moreover, the advantage of ALT for clinicians seems to differ according to the causative organism. Indeed, although some molecules, such as aminoglycosides, fluoroquinolones and tigecycline, have a broad spectrum of action, including gram-positive and gram-negative bacteria, their potentiality for ALT is limited by the lack of studies [55]. Some recent data, such as Funallera's work, suggest that aminoglycosides and fluoroquinolones as ALT could allow conservative management of CLABSI due to GNB infection with no signs of severity, but further studies are needed and better knowledge about their potential systemic toxicity, especially for gentamycin, is required.

In case of fungal infections, Amphotericin B showed good activity in biofilms caused by *Candida sp*. infections, but guidelines suggest that catheter removal is the best option [3, 27].

Among gram-positive CLABSI, only few data exist about conservative management of *S. aureus* infection, such as Fernandez-Hidalgo's work, which suggests that gentamycin could be a valid option for sterilizing catheters within 24 h of lock. However, as systemic signs and risks of complicated infections are frequent, catheter removal in case of *S. aureus* CLABSI is generally recommended [3]. In case of Enterococcal infections, Del Pozo et al. [56] showed the effectiveness of ALT among 3 out of 4 patients with *Enterococcus faecium* CLABSI, but the limited number of subjects requires prudent conclusions.

Therefore, the most promising indication for treating CLABSI with ALT appears to be CoNS-related infection, where systemic signs of infection are generally less severe and the introduction of novel molecules, such as DPT and tigecycline, improved the potential for cure without catheter removal. Although large prospective trials comparing DPT with vancomycin are lacking, the majority of comparative studies are in favor of DPT for its potent and rapid antibacterial capacity to inhibit bacterial biofilm and show a synergistic action with rifampin.

However, in vivo studies for DPT as ALT are scarce and questions concerning associated systemic treatment and duration of ALT remain unresolved.

Among other potential molecules for CoNS CLABSI, ethanol and taurolidine are two promising options, but few studies are available to confirm their place among ALT strategies and to exclude side effects.

Together with CoNS CLABSI, hemodialysis catheter infections appear as the other condition where ALT shows most chances of being successful and for which data are robust, with recent data also suggesting possible conservative management of GNB infections.

However, which kind of antibiotic, its dosage and treatment duration are points that still need to be elucidated.

Conflict of interest Authors declare that they do not have competing interests.

References

1. Ziegler MJ, Pellegrini DC, Safdar N. Attributable mortality of central-line associated bloodstream infection: systematic review and meta-analysis. Infection 2014 [Epub ahead of print].
2. Donlan RM. Biofilms and device-associated infections. Emerg Infect Dis. 2001;7:277–81.
3. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection, update by the Infectious Diseases Society of America. Clin Infect Dis. 2009. doi:10.1086/599376.
4. Funalleras G, Fernández-Hidalgo N, Borrego A, Almirante B, Planes AM, Rodríguez D, Ruiz I, Pahissa A. Effectiveness of antibiotic-lock therapy for long-term catheter-related bacteremia due to Gram-negative bacilli: a prospective observational study. Clin Infect Dis. 2011. doi:10.1093/cid/cir551.
5. Nesher L, Rolston KV. The current spectrum of infection in cancer patients with chemotherapy related neutropenia. Infection. 2014. doi:10.1007/s15010-013-0525-9.
6. O'Horo JC, Silva GLM, Safdar N. Anti-infective locks for treatment of central line-associated bloodstream infection: a systematic review and meta-analysis. Am J Nephrol. 2011. doi:10.1159/000331262.
7. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011. doi:10.1093/cid/cir257.
8. Wolf J, Allison KJ, Tang L, Sun Y, Hayden RT, Flynn PM. No evidence of benefit from antibiotic lock therapy in pediatric oncology patients with central line-related bloodstream infection: results of a retrospective matched cohort study and review of the literature. Pediatr Blood Cancer. 2014. doi:10.1002/pbc.25101.
9. Perez-Granda MJ, Barrio JM, Munoz P, Hortal J, Rincon C, Rabadan PM, et al. Ethanol lock Therapy (E-Lock) in the prevention of catheter related bloodstream Infectious (CR-BSI) alter major heart surgery (MHS): a randomized clinical trial. PLoS One. 2014. doi:10.1371/journal.pone.0091838.
10. Zhao Y, Li Z, Zhang L, Yang J, Yang Y, Tang Y, et al. Citrate versus heparin lock for hemodialysis catheters: a systematic review and meta-analysis of randomized controlled trials. Am J Kidney Dis. 2014;63:479–90.
11. The Joint Commission. Preventing central-line associated bloodstream infections. A global challenge, a global Perspective. http://www.jointcommission.org/assets/1/18/clasbi_monograph.pdf.
12. Fagan RP, Edwards JR, Park BJ, Fridkin SK, Magill SS. Incidence trends in pathogen-specific central line-associated bloodstream infections in US intensive care units, 1990–2000. Infect Control Hosp Epidemiol. 2013;34:893–9.
13. Sacks GD, Diggs BS, Hadjizacharia P, Green D, Salim A, Malinoski DJ. Reducing the rate of catheter-associated bloodstream infections in a surgical intensive care unit using the Institute for Healthcare Improvement Central Line Bundle. Am J Surg. 2014;207:817–23.
14. Dreesen M, Foulon V, Spriet I, Goosens GA, Hiele M, De Pourcq, et al. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: a systematic review. Clin Nutr. 2012;31:602–8.
15. Bestul MB, Vandenbussche HL. Antibiotic lock technique: review of the literature. Pharmacotherapy. 2005;25:211–27.
16. Flynn PM. Vascular access device infections. In: Patrick CC, editor. Clinical Management of infections in immunocompromised infants and children. Philadelphia: Lippincott, Williams and Wilkins; 2001. p. 212–23.
17. Raad I, Hanna H, Jiang Y, Dvorak T, Reitzel R, Chaiban G, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates embedded in biofilm. Antimicrob Agents Chemother. 2007;51:1656–60.
18. Aumeran C, Guyot P, Boisnoir M, Robin-Hennequin C, Vidal M, Forestier C, et al. Activity of ethanol and daptomycin lock on biofilm generated by an in vitro dynamic model using real subcutaneous injections ports. Eur J Clin Microbiol Infect Dis. 2013;32:199–206.
19. LaPlante KL, Mermel LA. *In vitro* activity of daptomycin and vancomycin lock solutions on staphylococcal biofilms

in a central venous catheter model. Nephrol Dial Transplant. 2007;22:2239–46.
20. Donlan RM. Biofilm formation: a clinically relevant microbiological process. Clin Infect Dis. 2001;33:1387–92.
21. Mekni MA, Bouchami O, Achour W. Ben Hassen A. Strong biofilm production but not adhesion virulence factors can discriminate between invasive and commensal *Staphylococcus epidermidis* strains. APMIS. 2012;120:605–11.
22. Chauhan A, Lebeaux D, Ghigo JM, Beloin C. Full and broad-spectrum in vivo eradication of catheter-associated biofilms using gentamicin-EDTA antibiotic lock therapy. Antimicrob Agents Chemother. 2012;56:6310–8.
23. Bookstaver PB, Gerrard KR, Moran RR. Clinical outcomes of antimicrobial lock solutions used in a treatment modality: a retrospective case series analysis. Clin Pharmacol. 2010;2:123–30.
24. Lee JY, Ko KS, Peck KR, Oh WS, Song JH. *In vitro* evaluation of the antibiotic lock technique (ALT) for the treatment of catheter-related infections caused by staphylococci. J Antimicrob Chemother. 2006;57:1110–5.
25. Fernández-Hidalgo N, Gavaldà J, Almirante B, Martín MT, Onrubia PL, Gomis X, Pahissa A. Evaluation of linezolid, vancomycin, gentamicin and ciprofloxacin in a rabbit model of antibiotic-lock technique for Staphylococcus aureus catheter-related infection. J Antimicrob Chemother. 2010. doi:10.1093/jac/dkp499.
26. Messing B, Man F, Colimon R, Thuillier F, Beliah M. Antibiotic-lock technique is an effective treatment of bacterial catheter-related sepsis during parenteral nutrition. Clin Nutr. 1990;9:220–5.
27. Schiffer CA, Mangu PB, Wade JC, Camp-Sorrell D, Cope DG, El-Rayes BF, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. Clin Oncol. 2013;31:1357–70.
28. Walraven CJ, Lee SA. Antifungal lock therapy. Antimicrob Agents Chemother. 2013;57:1.
29. Ramage G, Jose A, Sherry L, Lappin DF, Jones B, Williams C. Liposomal Amphotericin B displays rapid dose-dependent activity against *Candida albicans* biofilm. Antimicrob Agents Chemother. 2013;57:2369–71.
30. Raad II, Hachem RY, Hanna HA, Fang X, Jiang Y, Dvorak T, et al. Role of ethylene diamine tetra-acetic acid (EDTA) in catheter lock solutions: EDTA enhances the antifungal activity of amphotericin B lipid complex against Candida embedded in biofilm. Int JAntimicrob Agents. 2008;32:515–8.
31. Beigi AA, Khansoltani S, Masoudpour H, Atapour AA, Eshaghian A, Khademi EF. Influence of intralumenal and antibiotic-lock of vancomycin on the rate of catheter removal in the patients with permanent hemodialysis catheters. Saudi J Kidney Dis Transpl. 2010;21:54–8.
32. Van Praagh ADG, Li T, Zhang S, Arya A, Chen L, Zhang XX, et al. Daptomycin antibiotic lock therapy in a rat model of Staphylococcal central venous catheter biofilm infections. Antimicrob Agents Chemother. 2011;55:4081–9.
33. Estes R, Theusch J, Beck A, Pitrak D, Mullane KM. Activity of Daptomycin with or without 25 percent ethanol compared to combinations of Minocycline, EDTA, and 25 percent ethanol against methicillin-resistant *Staphylococcus aureus* isolates embedded in biofilm. Antimicrob Agents Chemother. 2013;57:1998–2000.
34. Dominguez-Herrera J, Docobo-Perez F, Lopez-Rojas R, Pichardo C, Ruiz-Valderas R, Lepe JA, et al. Efficacy of Daptomycin versus Vancomycin in an experimental model of foreign-body and systemic infection caused by biofilm producers and methicillin-resistant Staphylococcus epidermidis. Antimicrob Agents Chemother. 2012;56:613–7.
35. Meije Y, Almirante B, Del Pozo JL, Martin MT, Fernandez-Hidalgo N, Shan A et al. Daptomycin is effective as antibiotic-lock Therapy in a model of Staphylococcus aureus catheter-related infection. J Infect. 2014; doi:10.1016/j.jinf.2014.01.001.
36. Cirioni O, Mocchegiani F, Ghiselli R, Silvestri C, Gabrielli E, Marchionni E, et al. Daptomycin and Rifampin alone and in combination prevent vascular graft biofilm formation and mergence of antibiotic resistance in a subcutaneous rat pouch model of Staphylococcal infection. Eur J Vasc Endovasc Surg. 2010;40:817–22.
37. Del Pozo JL, Rodil R, Aguinada A, Yuste JR, Bustos C, Montero A, et al. Daptomycin lock therapy for grampositive long-term catheter-related bloodstream infections. Int J Clin Pract. 2012;66:305–8.
38. Tatarelli P, Parisini A, Del Bono V, Mikulska M, Viscoli C. Efficacy of daptomycin lock therapy in the treatment of bloodstream infections related to long-term catheter. Infection. 2014. [Epub ahead of print] PubMed PMID: 25112453.
39. Aybar Y, Ozaras R, Besirli K, Engin E, Karabulut E, Salihoglu T, et al. Efficacy of tigecycline and vancomycin in experimental catheter-related Staphylococcus epidermidis infection: microbiological and electron microscopic analysis of biofilm. Int J Antimicrob Agents. 2012;39:338–72.
40. de Rossi BP, Feldman L, Pineda MS, Vay C, Franco M. Comparative in vitro efficacies of ethanol-, EDTA- and levofloxacin-based catheter lock solution on eradication of *Stenotrophomonas maltophilia* biofilms. J Med Microbiol. 2012;61:1248–53.
41. New York-Presbyterian Hospital. Antibiotic (ALT) and ethanol (ELT) lock therapy for the management of central venous catheter-related infections 2011. www.cumc.columbia.edu/…/Antibiotic_and_Ethanol_Lock_Therapy_Medication_Use_Policy.
42. Dannenberg C, Bierbach U, Rothe A, Beer J, Körholz D. Ethanol-lock technique in the treatment of bloodstream infections in pediatric oncology patients with broviac catheter. J Pediatr Hematol Oncol. 2003;25:616–21.
43. Abu-El-Haija M, Schultz J, Rahhal RM. Effects of 70% ethanol locks on rates of central line infection, thrombosis, breakage and replacement in pediatric intestinal failure. J Pediatr Gastroenterol Nutr. 2014;58:703–8.
44. Mermel LA, Alang N. Adverse effects associated with ethanol catheter lock solutions: a systematic review. J Antimicrob Chemother. 2014. doi:10.1093/jac/dku182.
45. Leite B, Gomes F, Teixeira P, Souza C, Pizzolitto E, Oliveira R. Combined effect of linezolid and N-acetylcysteine against Staphylococcus epidermidis biofilms. Enferm Infecc Microbiol Clin. 2013;31:655–9.
46. LaPlante KL, Woodmansee S, Mermel LA. Compatibility and stability of telavancin and vancomycin in heparin or sodium citrate lock solutions. Am J Health Syst Pharm. 2012;69:1405–9.
47. Handrup MM, Moller JK, Schroder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. Pediatr Blood Cancer. 2013;60:1292–8.
48. Watson RW, Redmond HP, Mc Carthy J, Bouchier-Hayes D. Taurolidine, an antilipopolysaccharide agent, has immunoregulatory properties that are mediated by the amino acid taurine. J Leukoc Biol. 1995;58:299–306.
49. Shah CB, Mittelman MW, Costerton JW, Parenteau S, Pelak M, Arsenault R, et al. Antimicrobial activity of a novel catheter lock solution. Antimicrob Agents Chemother. 2002;46:1674–9.
50. Aslam S, Vaida F, Ritter M, Mehta RL. Systematic review and meta-analysis on management of hemodialysis catheter-related bacteremia. J Am Soc Nephrol. 2014;25:2927–41.
51. Joshi AJ, Hart PD. Antibiotic catheter locks in the treatment of tunnelled hemodyalisis catheter-related blood stream infection. Semin Dial. 2012; doi:10.1111.
52. Saxena AK, Panhotra BR, Al-hafiz AA, Sundaram DS, Abu-Oyun B, Al Mulhim K. Cefotaxime-heparin lock prophylaxis against

hemodialysis catheter-related sepsis among Stahylococcus aureus nasal carriers. Saudi J Kidney Dis Traspl. 2012;23:743–54.
53. Rosenblatt J, Reitzel R, Dvorak T, Jiang Y, Hachem RY, Raad II. Glyceryl trinitrate complements citrate and ethanol in a novel antimicrobial catheter lock solution to eradicate biofilm organisms. Antimicrob Agents Chemother. 2013;57:3555–60.
54. Dogra GK, Herson H, Hutchison B, Irish AB, Heath CH, Golledge C, Luxton G, Moody H. Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. J Am Soc Nephrol. 2002;13:2133–9.
55. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365–77.
56. Del Pozo JL, Alonso M, Serrera A, Hernaez S, Aguinaga A, Leiva J. Effectiveness of the antibiotic lock therapy for the treatment of port-related enterococci, Gram-negative, or Gram-positive bacilli bloodstream infections. Diagn Microbiol Infect Dis. 2009. doi:10.1016/j.diagmicrobio.2008.10.004.