Anti-Infective Locks for Treatment of Central Line-Associated Bloodstream Infection: A Systematic Review and Meta-Analysis

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Key Words

Antibiotic lock • Anti-infective lock • Catheter salvage • Central line-associated bloodstream infections

Abstract

Central line-associated bloodstream infections (CLABSI) are associated with considerable morbidity, mortality and economic costs. In most cases, catheter removal is considered an essential component of managing CLABSI. However, in patients with poor access, catheter salvage may have to be attempted rather than removal and replacement of catheters. Anti-infective lock therapy (ALT) – instilling an antibiotic or antiseptic into the catheter lumen – is a novel way of treating CLABSI while attempting to salvage the catheter. However, data on the efficacy of ALT for catheter salvage is limited. In this systematic review, we critically review the evidence regarding the use of ALT for catheter salvage. We identified 8 studies including a total of 396 patients that compared ALT with systemic antibiotic therapy alone or an alternate method of catheter salvage (guidewire replacement). We found that the combination of systemic antibiotics and culture-guided lock therapy was superior to systemic antibiotics alone (OR: 0.20, 95% CI: 0.10–0.39), with 10% of locked patients requiring replacement compared to 33% of

subjects without locks. There was a 20% relapse rate in the ALT group and a 30% relapse rate in the control group (OR: 0.43, 95% CI: 0.18–1.03). There was insufficient data on catheter exchange over a wire compared with ALT to permit conclusions. Our data support the use of ALT in conjunction with systemic antibiotics for catheter salvage. Large randomized controlled trials of ALT examining dose, dwell times and relapse rates stratified by infecting pathogen are needed.

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Introduction

Intravenous access is an essential lifesaving intervention in critically ill adults and children receiving parenteral alimentation, chemotherapy, antibiotic therapy and hemodialysis. Over 3 million central venous catheters are placed in the United States annually, and approximately 80,000 central line-associated bloodstream infections (CLABSI) occur [1]. CLABSI are associated with 12–25% mortality in intensive care patients, and increase costs of hospitalization by up to USD 56,000 [2].

In order for CLABSI to occur, microorganisms must first gain access to the device to form a sustainable biofilm and ultimately disseminate hematogenously. The

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initial colonization occurs in one of three ways: (1) extraluminal percutaneous tract infection, (2) intraluminally through manipulation of the catheter hub or lumen or (3) hematogenous spread from remote sources of infection such as pneumonia or urinary tract infection. In short-term catheters, the extraluminal route predominates, but CLABSI in long-term access devices tends to be intraluminal [1].

The preferred method of treatment for CLABSI is systemic antibiotic therapy in addition to catheter removal and replacement; however, in patients who need long-term access, catheter removal and replacement may not always be possible. In particular, long-term dialysis patients are prone to scarring of the vessels, which can make finding alternate sites for central access difficult or impossible.

Anti-infective lock therapy (ALT) was developed in the 1980s as an option for adjunctive treatment of CLABSI when catheter removal is not an option. The premise of the therapy is that for long-term catheters CLABSI is more likely to originate in the catheter lumen, and thus instillation of anti-infectives in the lumen for several hours a day may be useful for the treatment of CLABSI and to salvage the catheter [1]. This practice has been successful in preventing CLABSI [3] and is endorsed as a second-line therapy in the recent guidelines by the Infectious Diseases Society of America (IDSA) for management of CLABSI [1]. However, a systematic assessment of the utility of ALT for management of CLABSI is lacking. We undertook a systematic review and meta-analysis to determine the efficacy of ALT as a treatment of CLABSI.

Methods

Literature Search

A literature search was performed using PubMed, CINAHL, African Index Medicus, EMRO, Indmed, IMSEAR, LILCS, Pan-teliomon, Western Pacific Index Medicus, KoreaMed, Clinical-trials.gov, CRISP and REFDIC databases for the terms 'antibiotic lock' and 'anti-infective lock'. No language restrictions were applied. References were manually inspected and relevant articles obtained. When needed, study authors were contacted for further information. Searches were performed from December 2009 through February 2011. The search strategy is in alignment with PRISMA recommendations [4].

Inclusion/Exclusion Criteria

We included studies that compared ALT to systemic antibiotic therapy or to wire exchange, or both, for treatment of CLABSI. Studies that used the lock technique for prevention only were excluded. Because the goal of this review was to examine catheter salvage, studies that focused on routine catheter removal as a

treatment of CLABSI were excluded. Case series, case reports and other single-arm trials were excluded, as were review articles, in vitro studies and editorials.

Outcome Measures

Data on rates of catheter removal and incidence of relapse were abstracted from each study, as well as inclusion criteria, underlying conditions and individual study designs.

Data Analysis

Data analysis was performed using the Mantel-Haenszel fixed effect model for dichotomous data, and inverse variance fixed effect for continuous data. Heterogeneity was assessed with an I^2 statistic, where 0% indicates no heterogeneity and 100% indicates the highest level of heterogeneity. Publication bias was assessed using Egger's statistical test and a funnel plot. Data analysis was performed using Cochrane Database's Review Manager 5.1.0 software [5].

Results

Literature Search

The search strategy described above identified 383 studies. Of these, 272 specifically addressed antibiotic locks. Fifty-nine of these were basic science papers, 68 were review articles and guidelines, and 86 dealt exclusively with prevention. Forty-four were excluded for having no control arm, and three studies [6–8] were excluded for a comparison arm of routine catheter exchange. Eight relevant studies meeting inclusion criteria were identified and are listed in table 1 [9–16].

Study Characteristics

All eight studies included patients with long-term catheters ($n = 396$). Two studies included adult oncology patients, one studied pediatric oncology patients, two included adult parenteral nutrition subjects, and five addressed hemodialysis patients exclusively. The length of time that the access devices had been in place prior to infection was not reported, nor was the frequency with which the access devices were used.

Four studies were prospective interventions [12, 15], with one randomized controlled trial and two historically controlled prospective trials of ALT [9, 13]. Four were retrospective chart review studies [10–13, 16].

Lock solutions used in studies were highly variable, using 74% ethanol [10], third-generation cephalosporins [11, 13], aminoglycosides [11, 12], ciprofloxacin [11, 12] and imipenem-based solutions [12]. Most studies used ALT in conjunction with systemic therapy, with oral antibiotics in one study [9] and IV antibiotics in five [10, 11, 16, 17]. Concentrations varied widely as well, with studies

Table 1. Study characteristics

Study	Methods	Participants	Interventions	Outcomes	Notes
Messing et al. [16], 1988	retrospective chart review	adult home parenteral nutrition patients	treated with either 3 weeks methicillin, culture-guided antibiotic lock or a combination of the two	abatement of fever, and clearance of blood culture	
Dannenberg et al. [10], 2003	retrospective chart review	pediatric oncology patients with Broviac catheter infections	ethanol lock was compared with systemic antibiotic therapy guided by culture data	relapse and catheter removal	more neutropenics were in the comparison arm than the treatment arm.
Poole et al. [14], 2004	controlled interventional study	adult hemodialysis patient	compared culture-guided antibiotic lock therapy to wire-guided exchange	infection-free survival	more cases of <i>S. epidermidis</i> were in the lock arm
Rijnders et al. [15], 2005	randomized, placebo-controlled study	adult oncology	systemic antibiotics with culture-guided lock were compared to systemic antibiotics alone	catheter removal or relapse of infection	
Lee et al. [12], 2005	prospective interventional study	adult hemodialysis patients	culture-guided lock solution with systemic antibiotics was compared to systemic antibiotics alone	clearance of infection	more patients in the control arm had diabetes mellitus
Fortun et al. [11], 2006	retrospective chart review	adult TPN and oncology patients	culture-guided lock therapy compared systemic antibiotics alone	clinical symptoms, catheter removal	
Onder et al. [13], 2008	retrospective chart review	hemodialysis patients	antibiotic lock vs. wire-guided exchange	days of infection-free survival	
Beigi et al. [9], 2010	prospective interventional controlled study	adult chronic hemodialysis patients	vancomycin lock with systemic ceftriaxone compared to systemic vancomycin and amikacin	catheter removal, resolution of fever	

using as little as 1 mg/ml vancomycin [16] to 5 mg/ml vancomycin [9] in each lock. Timing of locks varied from a short course of 3 days [10] to a long course of up to 27 days [16]. Details of lock protocols and comparison treatment are available in table 2.

Comparison treatments were somewhat less varied with most trials using either IDSA-recommended systemic antibiotic regimens [10, 12, 15] or wire-guided exchange [13, 14] as controls. Three studies [9, 11, 16] used systemic antibiotic therapies, which were not defined by IDSA. Of note, one of these studies [16] used methicillin despite the majority of cases being Gram-negative infections. Comparison treatments are detailed in table 2.

No study specified the amount of time after CLABSI was diagnosed that the lock was started, nor specified if resistance to the lock solutions was predicted by culture data.

Not all papers reported microbiology of infection; of those that did, 59% of CLABSI cases were caused by Gram-positive organisms, 29% were caused by Gram-negative organisms and 11% were polymicrobial. Meth-

icillin-resistant *Staphylococcus aureus* (MRSA) was excluded from most studies; thus, only 5 patients in the meta-analysis had MRSA CLABSI. Multidrug resistant Gram-negatives and fungal infections were not reported. The microbiology of the infections is detailed in table 3.

Follow-up ranged between 6 weeks and 6 months. CLABSI was defined clinically in one study, [12] and with blood culture or differential time to positivity in the other seven studies. Treatment failure was clinically assessed in seven studies, and by tip culture confirming the same phenotypic bacterial infection as the index CLABSI in two studies [11, 15]. Only one study [10] specified an antibiotic flush, while in one [14] the lock was withdrawn and discarded between treatments; remaining studies did not specify if the lock solution was flushed or discarded. No studies looked at the concentration of locked antibiotics in serum.

All studies examining resistance data used this information to guide the choice of antibiotic lock agent. Resistance to lock solutions was not examined. Both studies

Table 2. Lock and comparison protocols

Study	Lock solution	Lock protocol	Comparison treatment
Messing et al. [16], 1988	organism dependent – <i>S. epidermidis</i> – vancomycin 2 mg/day – <i>Corynebacterium</i> – minocycline 0.4 mg/day – <i>Citrobacter</i> – amikacin 3 mg/day – <i>Klebsiella</i> – amikacin 3 mg/day – <i>Enterobacter</i> – amikacin 3 mg/day – <i>Serratia</i> – amikacin 3 mg/day – <i>Micrococcus</i> – amikacin	12 h/day for length prescribed by specific organism group I patients received ALT alone group II patients received ALT plus SAB lock protocol ranged from 14 days (<i>S. epidermidis</i> , <i>Citrobacter</i> , <i>Micrococcus</i>) to 27 days (<i>Serratia</i> spp.)	methicillin treatment for 3 weeks
Dannenberg et al. [10], 2003	2.3 ml ethanol 74%	lock was used for 20–24 h/day for 3 days on alternating lumens with SAB	SAB per IDSA guidelines
Poole et al. [14], 2004	four different solutions used – 1 ml vancomycin, 0.5 ml ceftazidime, 0.5 ml heparin – 1 ml vancomycin, 0.5 ml heparin, 0.5 ml NS – 1.0 ml ceftazidime, 0.5 ml heparin, 0.5 ml NS – 1.0 ml cefazolin, 0.5 ml heparin, 0.5 ml NS	antibiotic was infused into each port of the catheter after each dialysis session and withdrawn before the next concomitantly	wire-guided catheter exchange
Rijnders et al. [15], 2005	heparin with ceftazidime for GNR, heparin with vancomycin for GPC	lock was used daily for 7–14 days in conjunction with SAB	heparin plus SAB per IDSA guidelines
Lee et al. [12], 2005	sensitivity-guided solutions – vancomycin 100 mg/ml with heparin – imipenem 50 mg/ml mg with heparin – ciprofloxacin 2 mg/ml with heparin – ceftazidime 100 mg/ml with heparin	locks were instilled into both lumens of the dialysis catheter on completion of each dialysis session and withdrawn immediately prior to the next session	SAB per IDSA guidelines
Fortun et al. [11], 2006	GPC received vancomycin, GNR received gentamicin/ciprofloxacin according to protocol	organism dependent – CoNS-vancomycin lock for 12 days plus SAB – MSSA-vancomycin lock for 10 days plus systemic therapy with dicloxacillin for 10 days – GNR-gentamicin or ciprofloxacin lock for 14 days with SAB	organism dependent SAB – vancomycin for 12 days – MSSA-dicloxacillin for 3 days – GNR ceftazidime for 7 days – ceftoxime 14 days – cotrimoxazole for 12 days
Onder et al. [13], 2008	not specified	patients receiving locks were randomized into an early and late antibiotic lock group	wire-guided catheter exchange
Beigi et al. [9], 2010	vancomycin 500 mg in 100 ml NS	solution injected into each catheter lumen every 48 h for 7 days accompanied by cefixime oral antibiotics for 3 weeks	500 mg vancomycin in peripheral IV plus amikacin daily

Descriptions of individual studies' antibiotic lock and comparison arm protocols. MSSA = Methicillin-sensitive *Staphylococcus aureus*; GPC = Gram-positive cocci; GNR = Gram-negative rod; SAB = systemic antibiotics; NS = normal saline; CoNS = coagulase-negative staphylococci.

using catheter replacement used a wire-guided exchange technique.

Statistical Analysis

Results of the studies are reported in figures 1–3. Figure 1 shows the incidence of need for catheter removal and replacement; the combination of systemic antibiotics and culture-guided lock therapy was superior to systemic antibiotics alone (OR: 0.20, 95% CI: 0.10–0.39), with 10% of locked patients requiring replacement compared to 33% of subjects without locks. A low degree of hetero-

geneity was seen, with I^2 of 6% and $p < 0.00001$. Publication bias was not evident.

Figure 2 demonstrates rates of relapse with lock versus control treatments. Relapse was common in both groups, with a 20% relapse rate in the ALT group and a 30% relapse rate in the control group (OR: 0.43, 95% CI: 0.18–1.03). I^2 demonstrates no heterogeneity at 0%; $p = 0.54$. Publication bias was not evident.

Figure 3 reports the mean infection-free survival for antibiotic lock versus wire-guided catheter exchange. There was a mean difference of 63.75 (95% CI: 54.4–73.0)

Table 3. Microbiology of studies

	Bacterial isolates in lock group	Bacterial isolates in comparison group
Messing et al. [16], 1988	<i>S. epidermidis</i> (6), <i>Klebsiella oxytoca</i> (7), <i>Corynebacterium</i> (1), <i>Serratia marcescens</i> (1), <i>Citrobacter freundii</i> (2), <i>Enterobacter</i> spp. (4), <i>Micrococcus</i> (3)	<i>S. epidermidis</i> (2)
Dannenberg et al. [10], 2003	GPC (25), GNR (4)	GPC (10), GNR (4), aerobic bacilli (1)
Poole et al. [14], 2004	<i>S. aureus</i> (15), <i>S. epidermidis</i> (29), GNR (17), polymicrobial (5), other (2)	<i>S. aureus</i> (18), <i>S. epidermidis</i> (18), GNR (22), <i>Enterococcus</i> (1), polymicrobial (7), other (3)
Fortun et al. [11], 2006	CoNS (14), <i>S. aureus</i> (3), <i>P. aeruginosa</i> (2)	CoNS (19), <i>Klebsiella</i> (1), <i>S. aureus</i> (4), <i>Stenotrophomonas</i> (1), <i>P. aeruginosa</i> (3), <i>E. coli</i> (1)
Rijnders et al. [15], 2005	CoNS (14), <i>E. Coli/Klebsiella</i> (2), <i>Streptococci</i> spp. (2), <i>Acinetobacter</i> (1), <i>Corynebacterium</i> (1), <i>Enterobacter</i> (1), <i>Bacillus cereus</i> (1)	CoNS (15), <i>E. coli/Klebsiella</i> (2), <i>Streptococci</i> (1), <i>Agrobacterium</i> (1), <i>S. aureus</i> (1), <i>Serratia</i> (1), <i>Corynebacterium</i> (1), <i>Acinetobacter</i> (1)
Lee et al. [12], 2005	MSSA (6), <i>Burkholderia picketii</i> (3), MRSA (5) <i>Burkholderia cepacia</i> (1), CoNS (5), <i>Enterobacter aerogenes</i> (1), <i>Pseudomonas</i> (3), <i>Acinetobacter calcoaceticus-baumannii</i> complex	lock and comparison microbiology not differentiated
Onder et al. [13], 2008	GPC (57), GNR (41), polymicrobial (48)	not specified
Beigi et al. [9], 2010	MSSA, <i>Streptococcus</i> , <i>Klebsiella</i> spp., CoNS, <i>Acinetobacter</i> spp.	not specified

The number of distinct cases of each organism is listed in parentheses where available. MSSA = Methicillin-sensitive *Staphylococcus aureus*; CoNS = coagulase-negative staphylococci; GPC = Gram-positive cocci; GNR = Gram-negative rod; MRSA = methicillin-resistant *Staphylococcus aureus*.

days infection-free survival favoring antibiotic lock, though it should be noted that there were only two studies, with opposing conclusions and a high degree of heterogeneity ($I^2 = 97\%$). Publication bias was probable.

Discussion

Our data support the use of ALT in conjunction with systemic antibiotics for catheter salvage when catheter replacement is not an option, and clearly indicate that this is superior to using peripheral antibiotics alone. In our analysis, catheter salvage was possible in the majority of cases with ALT combined with systemic anti-infective therapy.

While a number of uncontrolled case series exist to support ALT for catheter salvage [17–20] in the setting of CLABSI, controlled data are scant. The only RCT is by Rijnders et al. [15] from 2005 comparing lock with systemic antibiotics to systemic antibiotics alone. Twenty-one patients received antibiotic lock (in addition to sys-

temic antibiotics) and experienced three relapse events, requiring catheter removal in three instances. One patient died, for a total of seven failures of the antibiotic lock. Twenty-three patients received antibiotics alone with nine relapses and thirteen catheter removals. Given the small sample size, this trial did not provide conclusive data on efficacy of ALT. One other prospective controlled trial in this field by Krishnasami et al. [8] was excluded from the meta-analysis above because the control arm was routine catheter replacement rather than another attempt at salvage. Like the Rijnders study, the study by Krishnasami et al. was largely supportive of ALT, reporting a 51% success rate of the lock.

Current IDSA guidelines support the use of adjunctive ALT for catheter salvage in patients with infected lines with organisms other than *Candida* spp. and *S. aureus*, both of which are noted to have very low salvage success rates in case series [8, 18, 21]. There is insufficient evidence to routinely use ethanol locks as therapy, given the single study available [1].

Fig. 1. Incidence of catheter replacement. Subgroup 1 describes subjects in whom lock solutions were used alone; subgroup 2 describes those subjects who were treated with a lock in conjunction with an antibiotic. Statistical analysis was performed with RevMan software [5].

Placing ALT into context for use as adjunctive therapy for CLABSI is important. ALT should not be used in patients with evidence of exit site or tunnel infection, metastatic infection, or hemodynamic instability, and such patients were largely excluded from clinical studies. One study [15] noted significant barriers to using antibiotic locks, which limit its efficacy. The most important barrier was that in patients who needed their access used for most of the day, line time was insufficient for a prolonged dwell. Finally, the evidence for ALT exists mainly for treatment of coagulase-negative staphylococci. ALT is not recommended for CLABSI with *S. aureus* or yeast, or resistant Gram-negative pathogens. In general, line salvage is not recommended in cases of infection with these pathogens. In all cases of ALT for treatment, blood cultures to ensure clearance of bacteremia should be drawn at the beginning and end of therapy and in between if there is lack of clinical improvement. If blood cultures remain positive, attempts at catheter salvage should be abandoned.

Our analysis has a number of limitations – principally the lack of controlled data on ALT efficacy. Most available studies used historical controls with their attendant limitations with an overall small sample size. This limited our ability to examine the efficacy of lock solutions for specific patient populations, device types or specific pathogens. Secondly, there was wide variability in the concentrations and type of lock employed and in the microbiology of CLABSI. Thirdly, lack of standardization of the comparator was another limitation, as some systemic antibiotic regimens may have been more or less potent than others.

Because of the heterogeneity of data, small number of studies and widely diverging results of the two available studies, no conclusion can be made regarding wire-guided exchange versus antibiotic lock therapy. The reason for the discrepant findings is not clear: the wire exchange methodology between the two studies was not apparently different, and both studies used similar lock protocols. More Gram-negative and polymicrobial infections were

Fig. 2. Incidence of relapse: incidence of subjects who were treated with lock alone or lock and systemic antibiotics. No statistically significant difference is seen.

Fig. 3. Days of infection-free survival: although there is a statistically significant trend towards longer infection-free survival with ALT vs. wire-guided exchange, the high degree of heterogeneity between the studies should be noted.

reported in the study by Poole et al. [13], and this may be a contributing factor to the disagreement with the study by Onder et al. [14].

Other potentially promising approaches may include combinations of ALT and wire exchange. We did not identify any studies that used this approach, but it may be worth considering for a pathogen where ALT alone is unlikely to effect salvage and line removal is not an option. While ALT is a potentially promising therapy for line salvage and CLABSI, further research is necessary to determine optimal timing, dosing, predictors of success and duration of treatment.

A final consideration is that the concentrations of antibiotics in these studies may have been insufficient. At least one in vitro study [22] has demonstrated a clear benefit to concentrations as high as 5 mg/ml, a level achieved

in only one of these studies [9]. Further in vivo evaluation of higher concentrations may yield more clear support of ALT.

In conclusion, while our analysis shows that ALT is a promising approach to catheter salvage, the body of literature is scant and further study is needed to examine the role of ALT as a routine adjunctive approach to CLABSI treatment. In particular, the efficacy of ALT should be studied for a differential effect by pathogen, and the role of wire exchange should be examined.

Disclosure Statement

None of the authors have any conflicts of interest to disclose.

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