Citraflow™, Sodium Citrate Prefilled Syringes

Clinical evidence compendium

A summary of the clinical evidence of the effectiveness of Sodium Citrate in locking and flushing VAD

Dear Reader,

Maintaining catheter patency and preventing catheter-related bloodstream infections (CRBSIs) are central goals in vascular access management. MedXL Citraflow™ prefilled syringes are specially designed to enhance best clinical practice for improved patient outcomes and greater clinical efficiency. With a full range of locking solutions, including 4%, 30% & 46.7 % Sodium citrate lock solution, MedXL's Citraflow™ pre-filled syringes provide clinicians with the best tools to meet their clinical needs.

Sodium Citrate lock solutions are recommended by the ERBP (European Renal Best Practice) guidelines and ASDIN (American Society of Diagnostic and Interventional Nephrology).

Citraflow™ 4%, 30% & 46.7 % sodium citrate prefilled syringes provides equivalent catheter patency while offering an improved safety profile, reduction in the risk of CRBSIs and prevention of biofilm formation.

This evidence summary was compiled in order to facilitate the reader's ease of accessing the literature pertinent to sodium citrate lock solution. All studies in this compendium were found via a literature search and are provided as a courtesy to you, the reader.

All information in this summary was current as of September 2019 and MedXL is not liable for any inaccuracies therein.

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Studies evaluating the effect of different concentration of sodium citrate lock solution as an alternative to heparin in maintaining catheter patency:

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2019	2016	2015
First Author	Huang [1]	Pittiruti [2]	Grudzinski [3]
Study Name	Reducing catheter-associated complications using 4% sodium citrate versus sodium heparin as a catheter lock solution.	Evidence-based criteria for the choice and the clinical use of the most appropriate lock solutions for central catheters (excluding dialysis catheters): a GAVeCeLT consensus.	Benefits and harms of citrate locking solutions for hemodialysis catheters: a systematic review and meta-analysis.
Method	A total of 120 patients were divided into four groups (30 patients per group) according to the use of catheter lock solution as follows: 6250 U/mL sodium heparin, 5000 U/mL sodium heparin, 2500 U/mL sodium heparin, and 4% sodium citrate. Coagulation function and the incidence of catheter occlusion hemorrhage, and catheter-related infections were recorded.	After the constitution of a panel of experts, a systematic collection and review of the literature has been performed, focusing on clinical studies dealing with lock solutions used for prevention of occlusion (Heparin, citrate, urokinase, r-TPA, normal saline) or for prevention of infection (citrate, ethanol, taurolidine, EDTA). Studies on central lines used for dialysis of pheresis, on peripheral venous lines and on arterial lines were excluded from this analysis. Studies on lock solutions used for treatment of obstruction or infection were not considered. The consensus has been carried our according to the Delphi method.	The GRADE approach has been used to systematic reviews and quality appraisal. Two reviewers performed data extraction independently and in duplicate. They pooled count data using generic inverse variance with random effects models, and used fixed-effect models when only two studies were available for pooling. Subgroups included low (<5%) vs. Higher (>30%) citrate.
Results	The different catheter lock solutions were significantly related to conduit blockage, hemorrhage, infection, and leakage levels. In the 4% sodium citrate group, the odds ratio was 0.688 for conduit blockage (95% confidence interval [CI], 0.206–2.297), 0.286 for hemorrhage (95% CI, 0.091–0.899), 0.266 for infection (95% CI, 0.073–0.964), and 0.416 for leakage (95% CI, 0.141–1.225) compared with the 6250 U/mL sodium heparin.	The panel has concluded that: (a) there is no evidence supporting the heparin lock; (b) the prevention of occlusion is based on the proper flushing and locking technique with normal saline; (c) the most appropriate lock solution for infection prevention should include citrate and/ or taurolidine, which have both anti-bacterial and anti-biofilm activity, with negligible undesired effects if compared to antibiotics; (d) the patient populations most likely to benefit from citrate/taurolidine lock are yet to be defined.	Compared with heparin, citrate catheter locking solutions were associated with significantly fewer bleeding episodes. Rates of death and bacteremia tended to be lower with citrate, but pooled effect estimates were not statistically significant. No significant differences in catheter exchange/replacement, thrombolysis, or all-cause hospitalization were evident between groups in any of the pooled analyses.
Conclusions	The solution 4% sodium citrate can effectively reduce the risk of catheter obstruction, bleeding, infection, and leakage better than sodium heparin in patients with long-term intravenous indwelling catheters.	The actual value of heparinization for non-dialysis catheters should be reconsidered. Also, the use of lock with substance with anti-bacterial and anti-biofilm activity (such as citrate or taurolidine) should be taken into consideration in selected populations of patients.	Our findings are consistent with those of a similar and recently published meta-analysis by Zhao et al., which also found significantly reduced bleeding rates, but no difference in survival, hospitalization, or catheter patency with citrate alone as compared with heparin
Journal Name	Journal of International Medical Research	JVA – Journal of vascular Access	Canadian Journal of Kidney Health and Disease

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2014	2014	2014
First Author	Parienti [4]	Clark [5]	Zhao [6]
Study Name	Quasi-Experimental Study of Sodium Citrate Locks and the Risk of Acute Hemodialysis Catheter Infection among Critically Ill Patients	Temporary Hemodialysis catheters: recent advances	Citrate versus heparin lock for hemodialysis catheters: a systematic review and meta-analysis of randomized controlled trials.
Method	This study compared the risks of dialysis catheter infection according to the choice of locking solution in the intensive care unit (ICU). A prospective quasi experimental study with marginal structural models (MSM) and 2:1 greedy propensity score matching (PSM) was conducted at nine university affiliated hospitals and three general hospitals.	This mini review focuses on techniques that reduce the complications of NTHCs and are relevant to the practice and training of nephrologists	A systematic review and meta-analysis was performed by searching in PubMed, EMBASE, Ovid, the Cochrane Library, and Web of Science databases and major nephrology journals.
Results	Our results support the concept of an antimicrobial catheter lock solution specifically a citrate solution, to prevent the risk of short-term catheter-associated infection risk among patients who require RRT in an ICU setting.	Overall, the evidence supports a recommendation that citrate (⩽4%) locks be favored over heparin locks for NTHCs. Currently, 4% citrate is used in most HD units in Canada in the form of prefilled 5 ml syringes (Citralok, MED-XL, Montreal, QC, Canada) 24 for patients with tunneled HD catheters. The extent to which it is used for NTHCs is unknown particularly given that NTHCs are often used in ICUs or other critical care areas. It should be noted that, in the United States, none of the most commonly used catheter-locking solutions, including heparin at the 1000 U/ml concentration, are approved by the Food and Drug Administration for use in HD catheters. This also includes 4% citrate which is only available in 250 or 500 ml bags and requires further preparation before being used as a catheter lock.	Pooled analyses found that citrate locks could significantly reduce the incidence of CRBSI (risk ratio [RR], 0.39; 95% CI, 0.27-0.56; $P < 0.001$)
Conclusions	Consistent with our hypothesis, the risk of dialysis catheter infection was lower with the use of sodium citrate locks in the ICU.	Citrate (⩽4%) catheter locks should be used for NTHCs rather than heparin. There is currently insufficient evidence to support the routine use of ACLs or specialized catheters with antimicrobial properties.	An antimicrobial-containing citrate lock is better than a heparin lock in the prevention of catheter-related infection, while citrate alone fails to show a similar advantage. Citrate locks of low to moderate concentrations, rather than high concentration, were superior to heparin locks in preventing CRBSI. Citrate locks also might decrease bleeding episodes.
Journal Name	American Society for Microbiology.	Kidney International	Am J Kidney Dis

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2013	2011	2010
First Author	Yon [7]	Lee [8]	Mokrzycki [9]
Study Name	Sodium citrate 4% versus heparin as a lock solution in hemodialysis patients with central venous catheters	Minimizing Hemodialysis Catheter Dysfunction: An Ounce of Prevention	Traditional and non-traditional strategies to optimize catheter function: go with more flow
Method	Data for patients receiving heparin lock solutions were collected from July 2008 to July 2009. Data on patients receiving sodium citrate 4% lock solution were collected from September 2009 through December 2010. Patients who were receiving the heparin lock solution who continued to have a CVC in September 2009 were transitioned from heparin to sodium citrate catheter 4% lock solution.	Several interventions including instillation of locking solutions and administration of systemic anticoagulation and antiplatelet agents are reviewed.	This review will focus on the etiology, prevention, and management of CVC-related malfunction
Results	Data were collected from 360 patient-months among 60 patients during the heparin treatment period and from 451 patient-months among 58 patients during the sodium citrate period. Thirty-three patients were common to both study groups. There were significantly more CRIs and CRIs per 1000 catheter-days in the heparin than the sodium citrate treatment group. Secondary outcomes of hospitalizations and catheter thrombosis were comparable. CRIs and thrombosis led to significantly more catheter exchanges or removals in the heparin group than the sodium citrate group.	Most efforts to prevent dialysis TC malfunction have focused on the instillation of locking solutions in TCs. Heparin and citrate prevent clot formation in dialysis TCs and are the most commonly used TC lock solutions. Thrombolytic agents have been recently shown to be more effective in reducing TC-related infections and improving TC patency.	There are advantages to citrate lock that make it a desirable option. One is that citrate has been associated with a lower bleeding event rate. Fewer systemic bleeding events were found using 4% citrate lock (7 in 32 patients) versus heparin lock (5000 U/ml) (21 in 29 patients) (P ¼ 0.035)35 in tunneled CVC. Other potential advantages of citrate lock include a reduction in biofilm formation, avoidance of HAAb formation, lack of interference with prothrombin assays, and lower costs. Although potential cost savings should be evaluated individually for dialysis facilities, an 80–85% reduction in costs was calculated using citrate in comparison with heparin in two Canadian studies.
Conclusions	In patients with long-term hemodialysis catheters, a lock solution of sodium citrate 4% was associated with fewer CRIs and similar effectiveness when compared with heparin 5000 units/mL.	Important areas of future research include development of modified TCs with new designs and thrombosis-resistant properties and novel locking solutions and interventions to prevent or reduce biofilm and fibrin sheath formation. Through translational research.	Catheter malfunction will continue to be a costly complication of CVC use and is primarily due to intraluminal thrombosis and/or extra luminal fibrin sleeve encasement. The timing of occurrence may assist in determining its etiology but late complications can occur early and early complications can occur late.
Journal Name	American Journal of Health System Pharmacy	International Journal of Nephrology	International Society of Nephrology

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2010	2010	2010
First Author	Ash[10]	Pierce[11]	Vanholder [12]
Study Name	Advances in Locking Solutions	Trisodium Citrate : An alternative to UFH for hemodialysis Catheter Dwells	Diagnosis, Prevention and Treatment of Haemodialysis catheter related Bloodstream Infections – A position statement of European Renal Best Practice (ERBP)
Method	This review will focus on the effectiveness of different locking solution.	This review evaluates Sodium citrate lock solution as an alternative to Heparin.	This text discusses various IDSA guidance with regards to vascular access and infectious diseases in haemodialysis patients.
Results	Several studies have demonstrated that 4% sodium citrate as a catheter lock maintains catheter patency at least as well as heparin.	Within the last decade, increasing evidence has shown an evolving role of citrates as alternatives to UFH as catheter locking solutions. The potential advantages of citrate catheter locking solutions include decreased hemodialysis catheter–related bloodstream infections (CRBSI), decreased rates of catheter thrombosis, reduced costs and lower risk of inadvertent systemic anticoagulation due to leakage of the locking solution into the bloodstream.	Recommendations are given with respect to tunneled vs non-tunneled catheters, prevention of infection relating to catheter insertion and position as well as nursing care, preventative antimicrobial catheter locks and catheter surface treatment, exit site dressings, intravenous catheter and blood cultures for diagnosis. It also touches upon management of catheter infection in patients receiving haemodialysis, antibiotic locks, and diagnosis and management of a CRBSI outbreak.
Conclusions	The practice of dialysis will be greatly aided by an antibacterial catheter lock that can be used routinely in all patients with tunneled CVCD. Although catheter access will still be less preferable than use of a fistula, at least the catheter will not create significant dangers of systemic infections if there is a catheter lock that maintains catheter patency while diminishing CRBSI, making it a safe access for use until the arteriovenous fistula has matured and allows suitable and safe dialysis access.	Studies using citrate 4% suggest equivalent efficacy to UFH, a lower risk of adverse drug events, and decreased costs. Citrate 4% alone provides safe and comparable antithrombotic activity without a significant risk of systemic anticoagulation, as seen with UFH. Additional factors such as costs of labor, available compounding facilities, stability, and costs associated with management of adverse outcomes should be considered when choosing a catheter locking solution.	ERBP recommendations: In view of the potential risks of spillover of the locking solution, associated risks (arrhythmias, toxicity, allergic reactions, and development of resistance to antibiotics) should be balanced with the benefits in terms of prevention of infection. Citrate locks have, for the time being, most extensively been studied. The 4% solution seems to offer at present the best benefit/risk ratio.
Journal Name	Endovascular Today	Pharmacotherapy	Nephrology Dialysis Transplantation

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2008	2008	2007
First Author	Moran [13]	MacRae [14]	Lok [15]
Study Name	Locking Solutions for Hemodialysis Catheters: Heparin and Citrate - A position paper by ASDIN	Citrate 4% versus Heparin and the Reduction of Thrombosis Study (CHARTS)	Trisodium citrate 4%—an alternative to heparin capping of haemodialysis catheters
Method	This review will focus on the effectiveness of Sodium citrate locking solution versus heparin.	Sixty-one prevalent hemodialysis (HD) patients dialyzing with a tunneled cuffed HD catheter were randomized in a pilot study to receive either heparin 5000 U/ml or citrate 4% as a locking agent after HD. The primary outcomes were the development of catheter dysfunction (defined as a blood pump speed <250 ml/min or the use of tissue plasminogen activator) and catheter-associated bacteremia. The secondary outcomes were the development of an exit-site infection or bleeding complications (either local or systemic).	The objective was to prospectively study the clinical effectiveness, safety and cost of citrate 4% vs heparin locking by comparing rates of CVC exchanges, thrombolytic use (TPA) and access associated hospitalizations during two study periods: heparin period (HP) (1 June 2003–15 February 2004) and Citrate Period (CP) 15 March–15 November 2004. Incident catheters evaluated did not overlap the two periods
Results	There is a wide variation in the use of solution to lock tunneled central venous catheters for dialysis. Some centers use undiluted heparin concentrations ranging from 1000 to 10,000 U/ml and other centers place from 1000 to 10,000 U per lumen. Based on available evidence, it appears that heparin 1000 U/ml or 4% sodium citrate are suitable choices for lock solution to maintain patency of tunneled central venous catheters for dialysis. Risks from systemic anticoagulation are lower with heparin 1000 U/ml and 4% sodium citrate compared with higher concentrations of heparin.	Citrate had comparable catheter dysfunction episodes to heparin (13/32 [41%] cases versus 12/29 [41%] cases, respectively). There were no differences in the development of catheter associated bacteremia (2.2/1000 catheter days citrate versus 3.3/1000 catheter days heparin group; P 0.607) or exit-site infection (2.2/1000 catheter days for both groups).	There were 176 CVC in 121 patients (HP) and 177 CVC in 129 patients (CP). The event rates in incident CVC were: CVC exchange 2.98/1000 days (HP) vs 1.65/1000 days (CP) (P¼0.01); TPA use 5.49/1000 (HP) vs 3.3/1000 days (CP) (P¼0.002); hospitalizations 0.59/1000 days (HP) vs 0.28/1000 days (CP) (P¼0.49). There was a longer time from catheter insertion to requiring CVC exchange (P¼0.04) and TPA (P¼0.006) in the citrate compared with the heparin lock group. Citrate locking costs less than heparin locking but a formal economic analysis including indirect costs was not done.
Conclusions	Based on available evidence, it appears that the following solutions are suitable choices for lock solution to maintain patency of tunneled central venous catheters for dialysis: • Heparin 1000 U/ml or • 4% Sodium citrate	The preliminary findings from our pilot study demonstrate that 4% citrate is effective in maintaining catheter patency and does not appear to have any increased incidence of infections. Because citrate is significantly cheaper and has a more favorable side effect profile than heparin, it can be considered a potentially better locking agent in HD catheters.	Citrate 4% has equivalent or better outcomes with regards to catheter exchange, TPA use and access-related hospitalizations compared with heparin locking. It is a safe and less expensive alternative. Randomized trials comparing these anticoagulants with a control group would definitively determine the optimal haemodialysis catheter locking solution.
Journal Name	Seminars in Dialysis - 2008	Clinical Journal of the American Society of Nephrology	Nephrol Dial Transplant

Table 1 Studies examining the Benefits of Sodium Citrate 4% Locking solutions for HD Catheters

Date of Publication	2007	2006
First Author	Grudzinski [16]	Shanks [17]
Study Name	Sodium citrate 4% locking solution for central venous dialysis catheters - an effective, more cost-efficient alternative to heparin	Catheter lock solutions influence staphylococcal biofilm formation on abiotic surfaces
Method	Our haemodialysis unit converted to locking all central venous haemodialysis catheters with sodium citrate 4% instead of heparin 10 000 U/ml. A retrospective analysis compared the outcomes of the year prior and after the conversion. Flow-related catheter exchange rate, prevalence of INR assay interference, tissue plasminogen activator (rt-PA) utilization rate, rate of bacteraemias and annual cost of locking agent were examined.	Lepirudin, low molecular weight heparin, tissue plasminogen activator, sodium citrate, sodium citrate with gentamicin and sodium ethylene diamine tetra-acetic acid (EDTA) were assessed for their effect on biofilm formation on polystyrene, polyurethane and silicon elastomer.
Results	During the study period, 30 925 and 37 139 catheter days were identified during the heparin and citrate years, respectively. The rate of flow-related catheter exchange was not different during the two periods (1.81 vs 1.88 per 1000 catheter days, P¼0.89). Falsely elevated INR values were eliminated with citrate and the rate of rt-PA treatments was similar during the two periods (4.1 vs 3.23 per 1000 catheter days respectively, P¼0.07). The number of bacteraemias was similar during the two periods (0.77 vs 0.94 per 1000 catheter days respectively, P¼0.36). There was an 85% reduction in the costs associated with catheter-locking therapy during the citrate period.	Sodium citrate at concentrations above 0.5% efficiently inhibits biofilm formation and cell growth of S. aureus and Staphylococcus epidermidis. Sub-inhibitory concentrations of sodium citrate significantly stimulate biofilm formation in most tested S. aureus strains, but not in CNS strains. Sodium EDTA was effective in prevention of biofilm formation as was a combination of sodium citrate and gentamicin. Low molecular weight heparin stimulated biofilm formation of S. aureus, while lepirudin and tissue plasminogen activator had little effect on S. aureus biofilm formation.
Conclusions	The pharmaco-economic benefits of sodium citrate 4% are well supported by this analysis. Furthermore, citrate offers several clinical advantages over concentrated heparin: citrate lock avoids heparin-associated bleeding complications, improves reliability of INR assays and provides an effective alternative for patients with suspected or confirmed heparin-induced thrombocytopenia.	This in vitro study demonstrates that heparin alternatives, sodium citrate and sodium EDTA, can prevent the formation of S. aureus biofilms, suggesting that they may reduce the risk of biofilm-associated complications in indwelling catheters. This finding suggests a biological mechanism for the observed improvement in catheter-related outcomes in recent clinical comparisons of heparin and trisodium citrate as catheter locking solutions. A novel and potential clinically relevant finding of the present study is the observation that citrate at low levels strongly stimulates biofilm formation by S. aureus.
Journal Name	Nephrol Dial Transplant (NDT)	Nephrol Dial Transplant

Table 2 Studies examining the Benefits of Sodium Citrate 30% & 46.7% Locking solutions for HD Catheters

Date of Publication	2014	2012	2011
First Author	Schilcher [18]	Davenport [19]	Bevilacqua [20]
Study Name	Loss of antimicrobial effect of trisodium citrate due to 'lock' spillage from haemodialysis catheters	Why do hypertonic citrate locks lead to dialysis catheter malfunction; more than a weighty problem?	Comparison of trisodium citrate and heparin as catheter-locking solution in hemodialysis patients
Method	Time–kill studies measuring the antimicrobial effect of citrate 46.7%, citrate 3% and citrate-free blood were performed with overnight cultures of Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus).	This text discusses the strategies to reduce the risk of catheter Infection.	Retrospective study on the infection data from the Infection and Adverse Event Prevention Control Program registry, which included all hemodialysis patients using long-term catheters from April, 2006 to March, 2008. During the first 365 days, catheters were locked with heparin (Heparin group) and, during the following 365 days, with 46.7% trisodium citrate (Citrate group).
Results	Citrate 46.7% reduced the number of E. coli by 2 log units but after 24 h, 106 CFU/mL were still present. Citrate 3% and citrate-free blood had no antimicrobial effect on E. coli. Citrate 46.7%, citrate 3% and citrate-free blood had scarce antimicrobial effect on S. aureus within 24 h.	In addition to these in vitro tests, the effect of using four different citrate lock concentrations was studied clinically in groups of 10 patients, all using the same catheter design, by examining the aspirate from the catheter after the 48 h interdialytic period. Protein deposition was found in all 10 patients using both the 46.7% and 20% citrate lock solutions, whereas none of the 10 patients using either 10% or 4% citrate lock solutions had any visible evidence of protein deposition.	The catheter-related bacteremia episodes were significantly lower and hospitalization time was significantly shorter in the Citrate group when compared with those in the Heparin group. A tendency towards a lower occurrence of access site infection-related hospitalization was observed in the Citrate group ($p = 0.055$), and no difference was observed in catheter thrombosis leading to dysfunction between groups.
Conclusions	Spillage of catheter lock solution leading to reduced intra-luminal citrate concentrations considerably reduces the antimicrobial effect of citrate 46.7% on E. coli. As none of the solutions tested had relevant antimicrobial effect on S. aureus, the antimicrobial effect of 46.7% citrate lock solution in vivo has to be seriously questioned.	Lower concentrations of citrate were not found to cause protein deposition, and clinically lower catheter lock concentrations of citrate have been reported to reduce catheter-associated bacteraemia rates without reports of increased catheter malfunction.	The use of 46.7% citrate solution effectively reduced bacteremia episodes and hospitalization in chronic kidney disease patients on hemodialysis with long-term catheters.
Journal Name	Nephrol Dial Transplant	Nephrol Dial Transplant	J Bras Nefrol

Table 2 Studies examining the Benefits of Sodium Citrate 30% & 46.7% Locking solutions for HD Catheters

Date of Publication	2011	2010	2008
First Author	Lagaac [21]	Bosma [22]	Winnett [23]
Study Name	Catheter Care Management in Haemodialysis	Reduction of Biofilm Formation with Trisodium Citrate in Haemodialysis Catheters: A Randomized Controlled Trial	Trisodium Citrate 46.7% Selectively and Safely Reduces Staphylocaccal Catheter-Related Bacteremia
Method	A retrospective study for haemodialysis (HD) patients receiving HD through CVC were identified using our electronic patient database from September 2006 to May 2011 have been identified.	In this study the influence of catheter locking with heparin and sodium citrate were compared on the in vivo intraluminal biofilm formation in haemodialysis catheters. Six patients were randomly assigned TSC 30% or heparin for catheter locking for the duration of one month. After removal, the catheters were dissected in three segments and examined by standardized scanning electron microscopy to assess quantitative biofilm formation.	On 1 July 2006, inter-dialytic catheter locking solution was changed from 5000 IU/ml heparin to Citralock™ (46.7% TSC) in all haemodialysis patients at Barts and the London Renal Unit dialysing through an incident or prevalent tunnelled catheter. Prospectively collected blood culture data for the 6 months prior to the switch and 3 months at the end of the first year of TSC use were analysed.
Results	The incidence of the dialysis line related infection has fallen by 75 % in the six months from September 2006 to March 2007, since TSC 46.7 % was introduced compared with a six-month period prior to its introduction.	Formation of an intralumial microbial biofilm is noted to play a significant role in the development of catheter related infections. It has been demonstrated that Trisodium citrate has superior antimicrobial effects over heparin for catheter locking.	A major fall in CRB rates was noticed with a change from heparin (2.13/1000 catheter-days) in 2006 to TSC (0.81/1000 catheter-days) in 2007. This was due to significant reductions in staphylococcal CRB, true for sensitive, methicillin-resistant and coagulase-negative staphylococci. No increase in catheter malfunction was observed.
Conclusions	Changing catheter lock from heparin to TSC 46.7 % will not work alone to prevent and decrease the rate of catheter-related bacteraemia infection (CRBI). It is essential to uphold best clinical practices; the use of sterile procedure in inserting lines and adequate catheter care using a unit-based central venous access device (CVAD) care record.	The study demonstrates that using TSC 30% for catheter locking reduces the formation of microbial biofilm in haemodialysis catheters and culture-positive colonization. It is likely that this is the explanation for the observed prevention of CRis by TSC locking.	We found that 46.7% TSC is a safe, convenient and highly effective catheter locking solution, leading to significant reduction in CRB largely by preventing Staphylococcal bloodstream infections. Given that Staphylococcus aureus in particular is associated with serious and often disseminated infection, TSC seems to be a powerful tool for dialysis units.
Journal Name	NHS Foundation Trust	Nephrol Dial Transplant	Nephrol Dial Transplant

Table 2 Studies examining the Benefits of Sodium Citrate 30% & 46.7% Locking solutions for HD Catheters



Date of Publication	2006	2005	2002
First Author	Mandolffo [24]	Weijmer [25]	Weijmer [26]
Study Name	Catheter Lock Solutions: It's time for a change	Randomized, Clinical Trial Comparison of Trisodium Citrate 30% and Heparin as Catheter Locking Solution in Hemodialysis Patients	Superior Antimicrobial Activity of Trisodium Citrate Over Heparin for Catheter Locking
Method	In this study, we reviewed alternative solutions to heparin for locking HD CVCs. Several experiences have demonstrated that trisodium citrate (TSC) (30–47%), citrate (4%) and taurolidine (1.35%) solutions are effective and safe for the prevention of CRBI, while heparin stimulates biofilm formation. High citrate (47%) concentrations can also provide significant advantages in reducing catheter clotting, but controlled studies with larger populations are necessary to confirm and to extend the use of such solutions in clinical practice.	The study was conducted from April 2001 until September 2002 in nine dialysis units from the Netherlands and one from Belgium. Two units were situated in an academic center, seven were in a teaching hospital, and one was a private clinic. In the units, the overall average percentage of patients who relied on a catheter for vascular access was 14%.	Antimicrobial efficacy of four concentrations of TSC (2.2, 7.5, 15 and 30%) was compared with three equi-osmolal sodium chloride (NaCl) concentrations, unfractionated heparin 5000 IUuml and a solution of gentamicin 1 mguml in TSC 7.5%. We analysed antimicrobial properties by two classical in vitro susceptibility tests.
Results	Side effects with high sodium citrate concentrations have been reported only immediately after locking, the symptoms are probably caused by a temporary drop in ionized calcium and magnesium, but it is evident that these solutions should only be used by skilled and authorized personnel, with a rigorous protocol.	The percentage of catheters that had to be removed prematurely was 61% lower in the TSC-locked catheters compared with the heparin-locked catheters (28 versus 46%; relative risk [RR] 0.57; 95% confidence interval [CI] 0.38 to 0.85; P 0.005; The total number of catheters removed prematurely was reduced from 8.1 to 5.0 per 1000 catheter-days in the TSC group. Patency rates for tunneled catheters were much better with TSC versus heparin (RR 0.38, P 0.015).	Increasing TSC concentrations effectively killed the staphylococcal strains in both assays. For E.coli and P.aeruginosa complete killing was achieved only with TSC 30%. TSC 30% was also the only solution that significantly inhibited growth of C.albicans. Heparin manifested no antimicrobial effect of any significance. Adding gentamicin to TSC provided superior bacterial growth inhibition but had no effect on yeast growth. TSC solutions manifested superior antimicrobial activity compared with iso-osmolal NaCl solutions in both assays.
Conclusions	High citrate (47%) concentrations can also provide significant advantages in reducing catheter clotting, but controlled studies with larger populations are necessary to confirm and to extend the use of such solutions in clinical practice. Side effects with high sodium citrate concentrations have been reported only immediately after locking, the symptoms are probably caused by a temporary drop in ionized calcium and magnesium, but it is evident that these solutions should only be used by skilled and authorized personnel, with a rigorous protocol.	The results of this study show that for hemodialysis catheters, an interdialytic lock of TSC 30% is more effective in preventing premature removal than heparin. TSC reduced the risk for CRB by 75% and reduced the number of patients who died from this serious complication of hemodialysis catheter use. The findings were consistent among the subgroups of patients with tunneled and untunneled catheters. Our results are in agreement with a previous observational catheter-lock study that used high concentrations of TSC.	This in vitro study demonstrates superior antimicrobial activity of TSC, especially in higher concentrations, in contrast to heparin. The mechanism seems to differ from hyperosmolality. Ca2q and Mg2q chelating effects are probably more important. Adding gentamicin provided the most potent antimicrobial solution. However, for reasons concerning development of bacterial resistance and sensitization of the patient, continuous exposition to aminoglycosides seems not advisable.
Journal Name	The Journal of Vascular Access	J Am Soc Nephrol	Nephrol Dial Transplant

Table 3 Studies examining the Benefits of Citrate/Ethanol Locking solutions for HD Catheters

Date of Publication	2018	2015	2008
First Author	Vercaigne [27]	Vercaigne [28]	Takla [29]
Study Name	Long-Term Effect of an Ethanol/Sodium Citrate Locking Solution on the Mechanical Properties of Hemodialysis Catheters	An Ethanol/Sodium Citrate Locking Solution Compared to Heparin to Prevent Hemodialysis Catheter-Related Infections: a Randomized Pilot Study	Effectiveness of a 30% ethanol/4% trisodium citrate locking solution in preventing biofilm formation by organisms causing haemodialysis catheter-related infections
Method	Twenty-one HD catheters were used in this study. Three catheters, not exposed to locking solutions, underwent mechanical testing to determine baseline properties. Nine of the remaining 18 catheters were filled with normal saline and underwent mechanical testing in groups of three at 12, 24 and 36 weeks. Similarly, nine catheters were filled with the 30% ethanol/4% sodium citrate locking solution and tested in a similar manner.	This was a prospective, randomized, pilot study of 40 hemodialysis patients randomized to a 30% ethanol/4% sodium citrate or heparin 1000 units/mL locking solution. The primary outcome was identification of any serious adverse events over the study duration. Secondary outcomes included the rate per 1000 catheter days for catheter-related bloodstream infections (CRBSI), alteplase use, catheter dysfunction, and catheter removal.	Control and lock solutions (2.475 mL) were inoculated with 25 mL of bacterial suspension to yield initial densities of 1 106 cfu/mL. The CBD was filled with 250 mL of solution per well, placed on a rocker at 90 rpm and incubated at 378C for 72 h. Every 24 h growth medium was supplemented with fresh nutrient solution.
Results	The average force required to break the catheter lumens tended to be smaller in the catheters exposed to 30% ethanol/4% sodium citrate compared to saline controls at 12 and 24 weeks; however, there were no statistically significant differences between the groups after 36 weeks of exposure. The forces required to break these HD catheters are magnitudes greater than forces generated during a typical HD session.	Three serious adverse events were reported as possibly related to the catheter solutions. Only one CRBSI was observed during the study in the heparin arm. The rate of alteplase use was 1.5/1000 catheter days in the heparin arm compared to 2.8/1000 catheter days in the ethanol/citrate arm (rate ratio = 1.85, 90% CI 0.48, 7.07, p value = 0.45), while the rate of catheter dysfunction was 6.8/1000 catheter days in the heparin arm compared to 1.9/1000 catheter days in the ethanol citrate arm (rate ratio = 0.27, 90% CI 0.10, 0.74, p value = 0.04). Catheter survival to first catheter outcome was longer in the ethanol/citrate group compared to heparin and there were no catheter removals due to bacteremia or thrombosis.	The results of this study demonstrate that the 30% ethanol/4% trisodium citrate locking solution prevents biofilm formation in vitro. This solution could potentially be locked into haemodialysis catheters between dialysis sessions to prevent CRIs. The rapid kill of organisms by ethanol will not allow bacteria to become established and will therefore prevent bacterial biofilm formation.
Conclusions	We conclude that the 30% ethanol/4% sodium citrate locking solution had an effect on the mechanical properties of the catheters investigated, but not to the degree that would preclude further in vivo investigation. Further studies are necessary to determine the safety and efficacy of this catheter locking solution.	The ethanol/sodium citrate locking solution was safely used in this study. It appears to prevent CRBSI and may improve catheter survival compared to heparin.	The 30% ethanol/4% Trisodium citrate lock solution prevented the biofilm formation of all isolates of MRSA, MSSA, MRSE, P. aeruginosa and E. coli in vitro. Further studies are necessary to determine its efficacy and safety in the haemodialysis population.
Journal Name	The Journal of vascular access	The Journal of vascular access	Journal of Antimicrobial Chemotherapy

Table 4 Studies examining the stability and compatibility of Sodium Citrate locking solutions and antimicrobial solutions



Date of Publication	2015	2014	2013
First Author	Liu [30]	Moore [31]	Bookstaver [32]
Study Name	Anticoagulant therapies versus heparin for the prevention of hemodialysis catheter-related complications: systematic review and meta-analysis of prospective randomized controlled trials	Comparative Effectiveness of Two Catheter Locking Solutions to Reduce Catheter-Related Bloodstream Infection in Hemodialysis Patients	Stability and compatibility of antimicrobial lock solutions
Method	A systematic review and meta-analysis was performed of randomized controlled trials (RCT) that compared antimicrobial-containing or citrate-alone catheter lock solutions with heparin alone in patients undergoing hemodialysis with central venous catheters.	This prospective, multicenter, observational cohort study compared the effectiveness of two catheter locking solutions (gentamicin/citrate versus heparin) in 555 hemodialysis patients dialyzing with a tunneled cuffed catheter between 2008 and 2011.	Published stability and compatibility data on a growing array of solutions used for antimicrobial lock therapy (ALT) are reviewed.
Results	The present study shows that the use of citrate-alone lock solutions is associated with a significant reduction in the rate of CRB.	Antibiotic lock use was associated with a decreased risk of catheter-related bloodstream infection compared with heparin (risk ratio, 0.23; 95% confidence interval, 0.13 to 0.38 after multivariate adjustment). Cox proportional hazards modeling found that antibiotic lock was associated with a reduction in mortality (hazard ratio, 0.36; 95% confidence interval, 0.22 to 0.58 in unadjusted analyses; hazard ratio, 0.32; 95% confidence interval, 0.14 to 0.75 after multivariate adjustment). The rate of gentamicin-resistant organisms decreased (0.40/1000 person-years to 0.22/1000 person-years) in the antibiotic lock period (P=0.01).	Antimicrobials active against common CLABSI pathogens that may be appropriate for ALT include cefazolin, cefotaxime, ceftazidime, ciprofloxacin, daptomycin, gentamicin, linezolid, telavancin, ticarcillin–clavulanic acid, and vancomycin; validated data demonstrate the stability of these agents in solution with heparin or nonheparin anticoagulants over 72–96 hours or longer. Other antifungal agents and antiinfectives (e.g., ethyl alcohol) have been used in specific patients and ALT situations. The prolonged stability of several antimicrobial–additive combinations may allow for extended dwell times and less frequent lock solution exchanges.
Conclusions	This meta-analysis provides further evidence that antimicrobial-containing and citrate-alone lock solutions are superior to heparin in preventing CRB. Antimicrobial-containing lock solutions might also decrease clinical sepsis in hemodialysis patients. Solutions containing antibiotics + heparin or gentamycin + citrate may effectively reduce the incidence of CM. Citrate-alone lock solutions are associated with a lower incidence of bleeding episodes and ESI compared to heparin. Additional prospective, long-term RCTs on other types of catheter lock solutions versus heparin are required to confirm these findings.	The results of this study show that the use of a prophylactic, gentamicin/citrate lock was associated with a substantial reduction in catheter-related bloodstream infection and is the first to report a survival advantage of antibiotic lock in a population at high risk of infection-related morbidity and mortality.	Pharmacists' knowledge of diverse combinations of antimicrobial agents and additives in lock solutions, including several shown to be stable and compatible for extended periods, can help expand and optimize the use of ALT in both treatment and prophylactic modalities.
Journal Name	Int J Clin Exp Med	Clin J Am Soc Nephrol	Am J Health-Syst Pharm

Table 4 Studies examining the stability and compatibility of Sodium Citrate locking solutions and antimicrobial solutions

Date of Publication	2010
First Author	Dotson [33]
Study Name	Physical compatibility of 4% sodium citrate with selected antimicrobial agents
Method	Admixtures were prepared by mixing 4% sodium citrate with clinically relevant concentrations of antimicrobial agents (vancomycin 5 mg/mL, vancomycin 10 mg/mL, vancomycin 20 mg/mL, daptomycin 5 mg/mL, gentamicin 2.4 mg/mL, tobramycin 2.4 mg/mL, and linezolid 1 mg/mL). Three samples of each admixture were incubated (1) at 22-23 degrees C and exposed to light, (2) in a water bath at 37 degrees C and exposed to light, (3) at 22-23 degrees C and protected from light, and (4) in a water bath at 37 degrees C and protected from light. Visual compatibility, spectrophotometric absorbance, and pH were evaluated immediately after mixing (baseline) and at 8, 24, and 48 hours.
Results	There was no visual evidence of precipitation and no clinically important changes in pH observed during the 48-hour study period in any admixture. However, turbidity, based on absorbance, was noted with vancomycin 20 mg/mL at each time point.
Conclusions	No evidence of incompatibility was observed when vancomycin 5 mg/ mL, vancomycin 10 mg/mL, daptomycin 5 mg/mL, gentamicin 2.4 mg/mL, tobramycin 2.4 mg/mL, or linezolid 1 mg/mL was mixed with 4% sodium citrate as might occur in an antimicrobial lock. Vancomycin 20 mg/mL mixed with 4% sodium citrate displayed spectrophotometric evidence of incompatibility.
Journal Name	Am J Health Syst Pharm

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