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STATE-OF-THE-ART REVIEW

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Reevaluation of lock solutions for Central venous catheters in hemodialysis: a narrative review

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ABSTRACT

Background: A significant proportion of incident and prevalent hemodialysis patients have central venous catheters for vascular access. No consensus is available on the prevention of catheter dysfunction or catheter-related bloodstream infections in patients undergoing hemodialysis by means of catheter lock solutions.

Method: We reviewed the effects of single and combined anticoagulants with antibacterial catheter lock solutions or other antimicrobials for the prevention of thrombosis or infections in hemodialysis patients. Relative risks with 95% confidence intervals for trials of the same type of catheter locking solution were pooled.

Sources of information: We included original research articles in English from PubMed, EMBASE, SpringerLink, Elsevier and Ovid using the search terms 'hemodialysis,' 'central venous catheter,' 'locking solution,' 'UFH,' 'low molecular weight heparin,' 'EDTA,' 'citrate,' 'rt-PA,' 'urokinase,' 'gentamicin,' 'vancomycin', 'taurolidine,' 'sodium bicarbonate,' 'hypertonic saline' and 'ethanol' and 'catheter'.

Findings: Low-dose heparin lock solution (< 5000 U/ml) can efficiently achieve anticoagulation and will not increase the risk of bleeding. Low-concentration citrate (< 5%) combined with rt-PA can effectively prevent catheter infection and dysfunction. Catheter-related infections may be minimized by choosing the appropriate antibiotic and dose.

Limitations: There is a lack of follow-up validation data for LMWH, EDTA, taurolidine, sodium bicarbonate, ethanol, and other lock solutions.

Implications: Since catheterization is common in hemodialysis units, studies on long-term treatment and preventative strategies for catheter dysfunction and catheter-related infection are warranted.

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Introduction

Hemodialysis (HD) central venous catheters (CVCs) are divided into nontunnelled catheters and tunneled catheters. Nontunnelled catheters are the main vascular access for continuous renal replacement therapy and extracorporeal membrane oxygenation (ECMO), which is usually used in emergency HD treatment, whereas tunneled catheters are used extensively as a permanent vascular access in HD patients. The Kidney Disease Outcomes Quality Initiative (KDOQI) suggests that arteriovenous access (arteriovenous fistula or arteriovenous graft) takes precedence over CVC in most patients undergoing HD due to the lower infection risk associated with arteriovenous access use. However, the KDOQI does not have sufficient evidence to make such recommendations on the selection of the vascular access types based on their association with all-cause hospitalization or mortality [1].

Maintaining the function of the CVC is a prerequisite for successful extracorporeal blood purification therapy. Thrombosis and induced stenosis and infection are the main factors of CVC dysfunction, especially in long-term tunneled catheters. In a cohort of 1,041 patients who received outpatient maintenance HD therapy with a tunneled CVC, at 1 year, the risks of CVC-related bacteremia, dysfunction, and central stenosis were 9%, 15%, and 2%, respectively [2]. The occurrence of catheter dysfunction in tunnel HD is usually due to thrombosis, and a 'fibrin sheath' is the most common culprit [3]. CVCs are used in only 19% of the dialysis procedures in

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the United States but are responsible for 70% of the vascular access-related bloodstream infections [4].

In this review, we evaluated the pharmacological effects, clinical efficacy, and safety of CVC lock solutions to better comprehend the KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update [1]. We further address the scope and problems of various lock solutions used in CVC to promote the rational selection of CVC lock solutions.

Methods

PubMed, EMBASE, SpringerLink, Elsevier and Ovid were searched for relevant studies. The subject words included 'hemodialysis,' 'central venous catheter,' 'locking solution,' 'UFH,' 'low molecular weight heparin,' 'EDTA,' 'citrate,' 'rt-PA,' 'urokinase,' 'gentamicin,' 'taurolidine,' 'sodium bicarbonate,' 'hypertonic saline' and 'ethanol'. This review only considered articles in English. We focused on HD patients with CVC. In this review, we discuss the pros and cons of each lock solution and write an exhaustive narrative review of the hemodialysis CVC lock issue.

We analyzed the data using R software (version 4.1.2). Relative risks with 95% confidence intervals (CIs) for trials of the same type of catheter locking solution were pooled.

Heparin

Pros of using heparin catheter locks

Unfractionated heparin (UFH) is the most commonly used central venous lock solution clinically and is of economic and applicable value. The negatively charged heparin can bind to the positively charged arginine on the antithrombin III (AT-III) molecule, which can change the configuration of AT-III and expose the active site of arginine, which combines with a coagulation factor containing serine to become inactive, to achieve anticoagulation. Due to its powerful anticoagulant effect *in vivo* and *in vitro*, heparin can effectively prevent catheter thrombosis. Nevertheless, the KDOQI guidelines have not yet reached a consensus on the optimal concentration of UFH in lock solutions [1]. The recommended dose of heparin sodium lock solution is 1000–10000 U/mL.

In an RCT study comparing low-dose heparin (1000 U/mL) and high-dose heparin (5000 U/mL) to maintain the patency of newly imbedded tunnel catheters, there was no significant difference in blood flow, venous pressure, arterial pressure, or dialysis adequacy; no serious infection or bleeding events were observed [5]. In a prospective trial comparing a higher dose heparin lock (5000 U/mL) with a lower dose heparin lock (1000 U/mL), there was no difference in the cumulative catheter survival, catheter infection rate, or catheter patency; the use of low-concentration heparin resulted in significant savings despite the higher rt-PA use; and no major bleeding complications were observed in either group [6]. Renaud *et al.* [7] retrospectively observed 238 patients without high-risk bleeding after CVC implantation and found that there was no significant difference in the CVC-related infection-free survival, bleeding events, or insufficient blood flow among different doses of heparin (500, 1000, and 5000 U/mL).

However, there are some contradictory results in certain studies. In a retrospective study, Yevzlin *et al.* [8] found that concentrated heparin (5000 U/mL) was associated with increased major bleeding complications after tunnel catheter placement compared with low-dose heparin (1000 U/mL) or citrate catheter lock solutions ($p = 0.02$). A meta-analysis showed that compared with a high-concentration heparin lock ($\geq$ 5000 U/mL), a low-concentration heparin lock ($<$ 5000 U/mL) could significantly reduce the incidence of bleeding events and catheter-related infection, but there was no significant difference in the cumulative catheter survival and catheter dysfunction [9]. In addition, Holley *et al.* [10] and Thomas *et al.* [11] found that the use of rt-PA in the patients in the low-dose heparin (1000 u/ml) group was greater than that in the high-dose heparin (10000 U/mL) group and was not significantly related to catheter dysfunction. Despite the high use of rt-PA, the overall medical cost of 1000 U/mL heparin was significantly reduced. There were no differences in the secondary outcomes, including severe bleeding complications or hospitalization [10,11].

Cons of using a heparin catheter lock

A low-concentration lock solution is prone to catheter thrombosis and requires more use of rt-PA. However, theoretically, patients with a hypercoagulability tendency are suitable for a high-concentration heparin lock, but this will increase the risk of bleeding. Several studies have found that severe systemic anticoagulation usually occurs 10 min after 5000 U/mL of heparin lock solution enters the patient's blood circulation and lasts for at least 1–2 h after dialysis, resulting in the risk of bleeding [12,13]. Thompson and colleagues found similar results in their RCT study. There was a statistically significant increase in the measured activated partial thromboplastin time (APTT) and percent change in APTT at 10 min post-catheter heparin locking between the heparin 1,000 IU/ml group and the heparin

5,000 IU/ml group ($p < 0.001$) [14]. In an RCT study, there was a significant increase in APTT at 10 min after heparin locking in the low-dose (1000 U/mL) and high-dose (5000 U/mL) heparin groups, especially in the high concentration group, while there was no significant difference in the infection incidence and occlusion rate of the catheters. In the 5000 U/mL group, more patients had massive bleeding, and their hematocrit values were significantly decreased [15]. Hryszko *et al.* [16] compared heparin 5000 U/mL with heparin 2500 U/mL in an RCT and found that high-dose heparin and prolonged APTT 2 h after injection of the lock solution were independent risk factors for patients with bleeding events.

Studies *in vitro* suggest that approximately 20% of the lock solution will eventually leak *in vitro*, and the amount of leakage is related to the proportion of lock solution in the conduit volume [17,18]. In addition, *in vivo* studies have confirmed that 12% to 31.3% of the catheter lock will leak into the patient's blood 10 min after the injection of the lock solution, and 24.6% to 41.9% of the catheter lock will leak 48 h later [19]. The above studies confirmed that the systemic anticoagulation caused by high-dose heparin lock solution leakage *in vivo* will lead to the risk of bleeding.

We conducted a pooled analysis for the above studies that included all patient groups and that compared low-concentration heparin with high-concentration heparin. The pooled overall catheter dysfunction IRR was 0.89 (95% CI, 0.61–1.31), which was not significant. However, the pooled overall catheter-related bleed event IRR was 0.29 (95% CI, 0.14–0.56), favoring low concentrations of heparin (see Table 1).

In addition, *in vitro* studies suggested that heparin promoted the formation of staphylococcal biofilms and made the patients prone to CRBSI, which increased with increases in heparin concentration and stimulation time. A biofilm consists of bacteria or fungi that aggregate in a glycocalyx matrix of their own synthesis. Biofilms allow microorganisms to survive and proliferate despite host immunity and therapeutic doses of antibiotics, and this constitutes a permanent source of bacteremia and can favor the development of bacterial resistance [20]. Moreover, the bacteria associated with heparin-stimulating biofilms have a high level of resistance to vancomycin [21].

Another important adverse reaction is heparin-induced thrombocytopenia (HIT), which has a high incidence rate in the HD population (3.9–17.9%) [22]. Argatroban or sodium mesylate are used as alternative anticoagulants during HD. These drugs do not cross-react with heparin because their molecular structures are completely different, and they are likely to be used as an alternative locking solution for HIT patients [23].

Clinical recommendation

The American Society of Diagnostic and Interventional Nephrology recommends 1000 IU/mL heparin as the CVC lock solution [24]. Heparin can cause allergies or HIT and has no antibacterial effect (it may promote the formation of *Staphylococcus aureus* biofilms). Therefore, this study considers that 1000 IU/mL heparin lock solution should only be used in patients without a history of heparin allergy and HIT, as well as those with a low risk of infection. For patients with catheter obstruction or thrombosis, a higher concentration of UFH should be retained, and the concentration of common heparin should be 5000 U/mL. However, the changes in the APTT value should be monitored over time. In addition, it is necessary to pay attention to certain problems, such as the drug compatibility between heparin and other antibiotics, including aminoglycosides, β-lactams, glycopeptides, quinolones, and macrocyclic lipid antibiotics (such as gentamicin, cephalothin, vancomycin, ciprofloxacin, and adriamycin).

Low-molecular-weight heparin (LMWH)

Pros of using an LMWH catheter lock

LMWH is a heparin mixture that is depolymerized by chemical or enzymatic methods, with a molecular weight of 2000–12000 Daltons. LMWH only has an AT-III binding site without a thrombin-binding site, thus weakening the effects of antithrombin and preventing the prolongation of APTT. At the same time, LMWH shows less nonspecific binding with platelets, circulating plasma proteins, macrophages, and endothelial cells, which prolongs the half-life, enhances the antithrombotic ability of the vascular endothelium, and reduces the occurrence of HIT [25]. The data showed that the incidence of type II HIT in dialysis patients with heparin anticoagulation was between 2.8% and 12% [22], while in patients with LMWH anticoagulation, it was less than 1% [26].

Clinically, LMWH anticoagulation has great advantages in HD and is commonly used, but there are few studies on LMWH lock solutions. A crossover RCT study [27] compared UFH (5000 U/mL) and tinzaparin (2000 U/mL) as lock solutions and found that the alteplase use of the tinzaparin group decreased by 47.4% compared to the heparin group. The results show that tinzaparin may be a suitable substitute for HD CVC lock solution, but these results should be confirmed by conducting larger trials.

Table 1. Pooled outcomes from trials of catheter lock solutions that can be used selectively for catheter dysfunction prophylaxis.

Agents Studied, Reference	Patients (n)	Incidence Rate Ratio (IRR) (95% CI)	P value	Anticipated Incidence of Catheter Dysfunction (95% CI)		Tunneled catheters, %	Follow-up period
				Intervention Group	Control Group		
Low concentration heparin [5,6,11,14,15] (3 RCTs + 2 CCTs)	676	0.89 (0.61–1.31)	0.63	Heparin (1000–2500 U/ml): 18.35%	Heparin (5000–10000 U/ml): 20.11%	Tunneled catheters, 72.93%	2–3 months or until catheter removal
Tinzaparin [27] (1 RCT)	42	0.32 (0.01–8.26)	>0.99	Tinzaparin (2000 U): 1.37/1000 HD sessions	Heparin (5000 U/ml): 3.68/1000 HD sessions	Internal jugular vein, 97.6%	14 weeks
Citrate 4% [33–36] (1 RCT + 3 CCTs)	736	0.74 (0.55–0.98)	0.04	Citrate 4%: 30.37%	Heparin (5000 U/ml): 37.23%	Tunneled catheters, 100%	6–12months or until catheter removal
Citrate 30% [40] (1 RCT)	291	0.88 (0.49–1.57)	0.66	Citrate 30%: 18.24%	Heparin (5000 U/ml): 20.28%	Tunneled catheters, 34%	until catheter removal
Citrate 46.7% [41,42] (1 RCT + 1CCT)	297	1.82 (0.55–6.05)	0.40	Citrate 46.7%: 5.42%	Heparin (500–1500 U/ml): 3.05%	Tunneled catheters, 100%	6 months or until catheter removal
EDTA/Ethanol-Ca-EDTA [51,52] (2 RCTs)	387	1.47 (0.85–2.53)	0.16	EDTA/Ethanol-Ca-EDTA: 19.10%	Heparin (5000 U/ml): 13.83%	Tunneled catheters, 93.8%	3–8 months or until catheter removal
Weekly rt-PA [57] (1 RCT)	225	0.47 (0.26–0.85)	0.013	rt-PA once weekly: 20.00%	Heparin (5000 U/ml): 34.78%	Tunneled catheters, 100%	6 months
Taurolock™ [102–104] (3 RCTs)	287	1.16 (0.55–2.30)	0.69	1.35% Taurolidine + 4% citrate: 10.65%	Heparin (5000 U/ml)+/Gent 40 mg/ml: 9.36%	Tunneled catheters, 79.4%	3 months or until catheter removal
TauroLock™-HEP500 [92,105] (2 CCTs)	301	0.29 (0.16–0.55)	<0.0001	1.35%Taurolidine + 4% citrate + Heparin (500 U/ml): 10.12%	TauroLock™/antibiotic + Heparin/Heparin: 27.82%	Tunneled catheters, 100%	6 months
TauroLock™-U25,000 [107–109] (3 RCTs)	351	0.47 (0.25–0.87)	0.016	1.35% Taurolidine+ 4% citrate + urokinase (25000 U) once weekly: 9.88%	TaurolockHEP/4% citrate: 18.99%	Tunneled catheters, 100%	6 months or until catheter removal
Ethanol/+Heparin [111–114] (4 RCTs)	568	3.40 (1.83–6.49)	<0.0001	Ethanol + Heparin: 12.69%	Placebo/Heparin: 4.10%	Tunneled catheters, 81.9%	6 months or until catheter removal
Hypertonic saline + heparin [115] (1 RCT)	56	1.64 (0.40–6.98)	0.69	26% NaCl + Heparin: 15.38%	Standard heparin: 10.00%	Tunneled catheters, 100%	until catheter removal
7.5% NaHCO3 [118,119] (2 RCTs)	278	6.03 (2.40–14.57)	<0.0001	7.5% NaHCO3: 9.79%	Heparin (2500 U/ml): 1.77%	Tunneled catheters, 42.4%	6 weeks or until catheter removal

Cons of using an LMWH catheter lock

LMWH has potency, is easy to administer, has predictable clinical effects, and has few side effects [28]. Therefore, it is recommended as the preferred anticoagulant in dialysis patients, but this advantage does not exist when it is used as a lock solution. LMWH has a low risk of bleeding because it cannot directly inhibit the effect of antithrombin, but its anticoagulant effect is only partially blocked by protamine when there is a risk of bleeding [29]. Moreover, in terms of pharmacokinetics, LMWH has a longer half-life, but this also means that the LMWH lock will affect the coagulation state for a longer time when leaking into the patient's systemic circulation [30]. In terms of health economics, the price of LMWH is significantly higher than that of UFH. Therefore, in theory, LMWH is not suitable as a CVC locking solution.

Citrate

Pros and cons of using citrate

Trisodium citrate (TSC) is also an alternative anticoagulant used extensively in clinical blood purification treatments. Unlike heparin, the anticoagulant mechanism of TSC is to chelate calcium ions in the blood to form insoluble soluble complex calcium citrate, which can reduce the number of active calcium ions in the blood, prevent the transformation of prothrombin to thrombin, and inhibit the transformation of fibrinogen to fibrin, thereby achieving a good anticoagulant effect [31]. Compared with the risk of bleeding caused by the leakage of a heparin lock, sodium citrate solution entering the blood does not produce a systemic anticoagulant effect and reduces the tendency of systemic bleeding because citrate can be quickly metabolized into bicarbonate *in vivo* [32]. In addition, *in vitro* studies have shown that citrate alone can effectively inhibit biofilm formation and bacterial growth, but citrate alone at a concentration higher than 30% can completely kill bacteria, possibly without completely eradicating preexisting biofilms [30].

Clinical studies have shown that 4% sodium citrate is as effective as heparin in preventing hemodialysis catheter thrombosis. MacRae *et al.* [33] compared citrate 4% with heparin (5000 U/mL) and found no significant difference in the incidence of catheter dysfunction and the risk of CRBSI, but the incidence of bleeding decreased. Grudzinski *et al.* [34] found that 4% citrate was associated with less need for thrombolysis. Although this did not reach statistical significance, more clots were observed during dialysis, and there was no reduction in bacteremia [34]. However, Lok *et al.* [35] prospectively observed that the catheter exchange rate, the use of rt-PA rate, incidence of bacteremia and hospital stay were significantly decreased after replacing a 5000 U/mL heparin lock solution with a citrate 4% lock. Yon *et al.* [36] also found that CRBSI, catheter exchange, and the extraction rate (due to infection and/or thrombosis) decreased significantly after replacement with a citrate 4% lock. The above studies were analyzed by comparing citrate 4% with high-concentration heparin and showed that the overall catheter dysfunction IRR was 0.74 (95% CI, 0.55–0.98), and the overall catheter-related infection IRR was 0.59 (95% CI, 0.41–0.85), both of which showed the benefits of using citrate 4%. (see, Tables 1 and 2)

However, Yahav *et al.* [37], in a systematic review of 7 trials (818 patients; 75185 catheter days), found that citrate catheter lock (with or without antibiotics) significantly reduced the infection rate by 64% and the catheter removal rate by 44% but had no effect on catheter thrombosis. Chen *et al.* [38] reviewed 21 studies (4832 patients, 318,769 catheter-days) and found that the incidence of catheter-related bloodstream infections (CRBSIs) and exit-site infections (ESIs) was significantly lower in citrate-based regimens than in heparin-based regimens. No significant difference in preserving catheter function or all-cause mortality was found between the two groups [38]. Zhao *et al.* [39] analyzed 13 studies (1,770 patients; 221,064 catheter-days) and found that overall there is a large benefit to the use of citrate in combination with other antimicrobial solutions, instead of using citrate alone even at the highest concentrations, over heparin in the prevention of CRBSI.

Nevertheless, as for the anticoagulation mechanism, compared with heparin, high concentrations of citrate provide local anticoagulation by chelating calcium ions in the blood and reducing the bleeding risk. As a catheter lock, it has considerable anticoagulation advantages. Weijmer *et al.* [40] found that 30% citrate significantly reduced the incidence of catheter-related bacteremia and bleeding complications caused by accidental systemic heparinization, when compared with 5000 U/mL heparin. A retrospective study confirmed that a 46.7% citric acid lock solution reduced the incidence of catheter bacteremia and hospitalization rate in long-term dialysis patients, as compared with 1500 U/mL heparin [41]. In a prospective randomized controlled study, compared with 5% heparin, 46.7% citric acid showed no significant difference in CRBSI, catheter exit infection, or hospitalization rate, but the number of patients requiring the thrombolytic agent urokinase (u-PA) increased. The cumulative survival rate of the catheter decreased by 15% at 6 months; 34% of

Table 2. Pooled outcomes from trials of catheter lock solutions that can be used selectively for CRBSI prophylaxis.

Agents Studied, Reference	Patients (n)	Incidence Rate Ratio (IRR) (95% CI)	P value	Anticipated Incidence of CRBSI (95% CI)		Tunneled catheters, %	Follow-up period
				Intervention Group	Control Group		
Citrate 4% [34–36] (3 CCTs)	675	0.59 (0.41–0.85)	0.005	Citrate 4%: 0.7/1000 cath.days	Heparin (5000 U/ml): 1.2/ 1000 cath.days	Tunneled catheters, 100%	12 months or until catheter removal
Citrate30% [40] (1 RCT)	291	0.26 (0.13–0.55)	0.0001	Citrate 30%: 1.1/1000 cath.days	Heparin (5000 U/ml): 4.1/ 1000 cath.days	Tunneled catheters, 34%	until catheter removal
Citrate 46.7% [41] (1 CCT)	65	0.05 (0.01–0.40)	<0.0001	Citrate 46.7%: 0.2/ 1000 cath.days	Heparin (1500 U/ml): 3.3/ 1000 cath.days	Tunneled catheters, 100%	until catheter removal
Citrate 5% [44] (1 CCT)	28	0.59 (0.29–1.19)	0.137	5% sodium citrate: 1.33%	10% sodium citrate: 2.25%	Tunneled catheters, 100%	3 months
EDTA/Ethanol-Ca-EDTA [51,52] (2 RCTs)	387	0.29 (0.10–0.89)	0.0311	EDTA/Ethanol-Ca-EDTA: 0.1/ 1000 cath.days	Heparin (5000 U/ml): 0.5/ 1000 cath.days	Tunneled catheters, 93.8%	3- 8months or until catheter removal
Weekly rt-PA [57] (1 RCT)	225	0.29 (0.12–0.79)	0.011	rt-PA once weekly: 0.40 episodes/1000 patient-days	Heparin (5000 U/ml): 1.37 episodes/1000 patient-days	Tunneled catheters, 100%	6 months
Gentamicin (≧ 4mg/ml) [78,80,82] (3 RCTs)	203	0.06 (0.01–0.23)	<0.0001	Gentamicin + anticoagulant: 0.2/1000 cath.days	Heparin/Tau 1.35%-citrate 4%: 4.0/1000 cath.days	Tunneled catheters, 53.1%	3 months or until catheter removal
Gentamicin (0.32 mg/ml) [84–85] (1 RCT + 1 CCT)	858	0.26 (0.19–0.37)	<0.0001	Gentamicin + anticoagulant: 0.4/1000 cath.days	Heparin (1000 U/ml): 1.5/ 1000 cath.days	Tunneled catheters, 100%	until catheter removal
Cefazolin + Gentamicin [90,91] (1 RCT + 1 CCT)	390	0.31 (0.19–0.50)	0.0001	Cefazolin + gentamicin + Heparin: 0.6/1000 cath.days	Heparin (1000 U/ml): 1.8/ 1000 cath.days	Tunneled catheters, 100%	7 months or until catheter removal
Vancomycin + heparin/ gentamicin [87,88] (1 RCT + 1 CCT)	163	0.16 (0.06–0.42)	<0.0001	Vancomycin + Heparin/ gentamicin: 0.50/ 1000 HD sessions	Routine TCC management/ Heparin: 2.9/ 1000 HD sessions	Tunneled catheters, 100%	12 months
Cefotaxime + heparin [48,94,95] (2 RCTs + 1 CCT)	316	0.44 (0.34–0.57)	<0.0001	Cefotaxime + heparin: 1.6/ 1000 cath.days	Heparin (5000 U/ml): 3.6/ 1000 cath.days	Tunneled catheters, 100%	12 months
Minocycline + EDTA [97] (1 RCT)	204	0.26 (0.10–0.70)	0.0043	Minocycline + EDTA: 1.1/ 1000 cath.days	Heparin (5000 U/ml): 4.3/ 1000 cath.days	Tunneled catheters, 27.8%	3 months
Cotrimoxazole + heparin [98] (1 RCT)	87	0.19 (0.04–0.86)	0.0230	Cotrimoxazole + Heparin: 0.58/ 1000 cath.days	Heparin (2500 U/ml): 4.4/ 1000 cath.days	Tunneled catheters, 100%%	12 months
Taurolock™ [101–104] (3 RCTs)	218	0.35 (0.18–0.66)	0.0008	1.35% Taurolidine + 4% citrate: 1.1/1000 cath.days	Heparin (5000 U/ml): 3.0/ 1000 cath.days	Tunneled catheters, 79.4%	3 months or until catheter removal
TauroLock™-HEP500 [92,105] (2 CCTs)	301	0.84 (0.53–1.36)	0.48	1.35%Taurolidine + 4% citrate + Heparin (500 U/ml): 1.2/1000 cath.days	TauroLock™/ antibiotic + Heparin /Heparin: 1.4/1000 cath.days	Tunneled catheters, 100%%	15 months or until catheter removal
TauroLock™-U25,000 [107–109] (3 RCTs)	351	0.34 (0.16–0.77)	0.0064	1.35%Taurolidine + 4% citrate + urokinase (25000 U) once weekly: 0.3/ 1000 cath.days	TaurolockHEP/4% citrate: 0.9/ 1000 cath.days	Tunneled catheters, 100%%	6 months or until catheter removal
Taurolock™ vs Antibiotic [92,103] (1 RCT + 1 CCT)	246	1.42 (0.75–2.79)	0.29	Taurolidine + citrate 4% /+Heparin: 1.5/ 1000 cath.days	Antibiotic + Heparin: 1.1/ 1000 cath.days	Tunneled catheters, 100%%	3 months or 15 months
Ethanol70%/+Heparin [111–114] (4 RCTs)	568	0.43 (0.23–0.78)	0.0068	Ethanoll70%/+Heparin: 0.8/ 1000 cath.days	Heparin/placebo: 1.8/ 1000 cath.days	Tunneled catheters, 100%	until catheter removal
Hypertonic saline [115] (1 RCT)	56	0.92 (0.21–3.94)	0.54	26% NaCl + Heparin: 1.1/ 1000 cath.days	Standard Heparin: 0.96/ 1000 cath.days	Tunneled catheters, 100%	until catheter removal
7.5% NaHCO3 [118,119] (2 RCTs)	278	0.07 (0.0066–0.394)	0.0004	7.5% NaHCO3: 0.1/ 1,000 cath.days	Heparin (2500 U/ml): 1.9/ 1,000 cath.days	Tunneled catheters, 42.4%	6 weeks or until catheter removal

patients needed to have the dose reduced, and 15% of patients stopped the trial due to abnormal taste and skin sensations [42]. Presently, there seems to be insufficient evidence to confirm that high-concentration citrate is better than heparin in CRBSI.

In vivo studies showed that 46.7% and 20% citrate could induce protein aggregation in the catheter after injection of these lock solutions, which have potential risk of inducing pulmonary embolism, while 10% and 4% citric acid did not [43]. A crossover RCT study from Europe compared 10% TSC with 5% TSC and found a reduction in nonocclusive thrombosis in the 10% citrate group per HD session. However, there was no significant difference in the incidence of u-PA thrombolytic therapy, and no adverse effects were reported [44]. In contrast, the 10% TSC lock solution is safe and can be recommended.

However, there is no evidence that the use of high concentrations of citrate alone is beneficial to maintain catheter patency and prevent CRSBI. Although Ash *et al.* [45] sealed the catheters with 2 mL of 23% citrate, and no adverse reactions were observed, Power *et al.* [42] reported that approximately 10% of patients complained that they had a 'metallic' taste or temporary tingling in their fingers shortly after approximately 6 mL of 46.7% citrate was injected into the central vein (approximately 10 mmoL/L). According to the U.S. Food and Drug Administration, an end-stage renal disease (ESRD) patient died of cardiac arrest shortly after receiving 5 mL of a 47% citrate lock solution after placing central venous tunnel catheters [46]. The reason for this is unclear; a drop in blood glucose reportedly as the single contributing factor is most significantly related to the symptoms of citrate-induced hypocalcemia [47]. Therefore, high concentrations of citrate may not be safe since the catheter tip embedded in the internal jugular vein is located at the inlet of the right atrium, and TSC provides local anticoagulation by binding Ca^{2+}. Even if a small amount of citrate enters the right atrium, it may also lead to a local reduction of calcium ions in myocardium, can interfere with myocardial contraction, and lead to serious pacemaker dysfunction and a fatal arrhythmia [48]. Another reason is that a hypertonic citrate lock solution can lead to a decrease in the calcium content in the local blood at the catheter outlet, metabolic acidosis, and a slight increase in PCO_2 [49]. Therefore, the authors believe that it is strictly prohibited to use a high-concentration citrate locking solution in patients with internal jugular vein catheters or liver failure.

Clinical recommendation

The KDOQI recommends the use of a low concentration citrate (< 5%) CVC lock solution, if feasible, to prevent CRBSI and CVC dysfunction [1]. The American Society of Diagnostic and Interventional Nephrology recommends the use of 4% citrate as an acceptable choice of CVC locking solution for patients who cannot tolerate heparin [24]. Since citrate locking solutions may induce cardiovascular events, low concentrations of citrate can be suitable for patients without serious arrhythmias, and high concentrations of citrate are not recommended for patients with internal jugular vein catheters or liver failure. Citrate can be used as the basic anticoagulant of combined antibacterial locking solution, provided that there is no incompatibility with the antibiotics and antibacterial agents used.

Ethylene diamine tetraacetic acid (EDTA)

Pros and cons of EDTA

Ethylenediaminetetraacetic acid (EDTA) has anticoagulant and antibacterial effects, but there is not enough evidence that suggests the use of EDTA as a lock solution alone. EDTA can chelate divalent metal ions such as Mg^{2+}, Ca^{2+}, Mn^{2+}, and Fe^{2+} and has an anticoagulant effect. In addition, EDTA tetrasodium has broad-spectrum inhibitory activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacteria, and can effectively kill all of the live bacteria in biofilms [50]. In a multicenter prospective randomized controlled study, 4% EDTA significantly reduced the colonization of tunnel CVC compared with heparin 5000 U/mL, but the reduction rate of CRBSI was not significant and was associated with a higher thrombolysis rate. Its safety is equivalent to that of heparin locking solutions [51]. A RCT, including 270 hemodialysis patients with a prevalent CVC and that compared an antimicrobial catheter lock, showed that the use of a trimethoprim antibiotic, ethanol, and a Ca-EDTA lock solution significantly reduced the incidence of CLABSI than heparin 5000 U/mL ($p < 0.03$) and that the use of thrombolytics increased (40%vs12%, $p < 0$ .001), but the rates of catheter removal did not differ [52]. However, Ouellet [53] found that in a group of maintenance HD patients with catheter dysfunction, the replacement of 4% citrate with 4% tetrasodium EDTA resulted in a significant reduction in the use of alteplase. The pooled analyses of EDTA-contained lock solution versus heparin lock solution show that the incidence of CRBSI decreased by 71%, but no there was no significant decrease in the catheter dysfunction incidence ($p = 0.16$).

Clinical recommendation

EDTA and metal chelation agents play a significant role in reducing the occurrence of catheter CRBSI. However,

they are not equivalent to heparin in maintaining catheter patency, and they are not inferior to sodium citrate. Due to the lack of adequate research evidence, the KDOQI guidelines do not recommend EDTA alone as a locking solution. However, EDTA is rarely incompatible with common preservatives/antibiotics and can be used as a basic anticoagulant along with other antibiotics.

Plasminogen activators

Pros and cons of plasminogen activators

Plasminogen activators such as streptokinase (SK), rt-PA and its derivatives, single-chain u-PA, or double-chain u-PA are commonly used to treat CVC thrombosis clinically. Streptokinase may cause severe bleeding events and allergic reactions [54], so it is rarely used as a catheter lock solution for clinical research. Tissue plasminogen activator alteplase (rt-PA) and its derivatives and single-chain u-PA have fibrin binding sites, which can directly activate plasminogen and convert it into plasmin, and rt-PA can strongly dissolve fibrin by protein hydrolysis and single peptide bond breaking [55]. Alteplase has a weak antifibrinogen effect, a strong antithrombotic effect, and a low bleeding risk.

A single randomized crossover trial involving 12 patients undergoing hemodialysis showed that a 2 mg rt-PA lock in each lumen decreased the incidence of thrombotic events by 20% compared with a 2000 units/ml heparin lock in each lumen [56]. The large multicenter trial pre-CLOT that included 225 participants compared 1 mg rt-PA lock once a week plus a heparin lock after the other dialysis sessions, in which a heparin lock was used after each dialysis session for 6 months follow-up. The results showed that compared with the heparin group, the incidence of catheter dysfunction in the rt-PA lock group decreased by 53% ($p = 0.01$), and the CRSBI incidence decreased from 1.37/1000 catheter days to 0.4/1000 catheter days ($p = 0.01$). Despite early discontinuation and high withdrawal rates (114/225 patients), this study provides evidence for the use of rt-PA as a catheter lock [57]. In addition, a multicenter cohort study in Canada compared the prophylactic use of rt-PA lock once a week and a 4% citrate lock after each HD session in high-risk patients with TCC-TD (thrombosis dysfunction) or with a history of CRBSI and suggested that rt-PA lock solution reduced the use of thrombolytic agent by 61%, but rt-PA had no significant effect on the incidence of catheter removal [58]. Despite the higher cost of rtPA, and after considering the hospitalization expenses caused by CRBSI and catheter failure, the intermittent use of rtPA lock is still a good choice for patients with suspected catheter failure, thrombosis or catheter-related bacteremia.

In addition, recombinant TPA has primarily been used as a thrombolytic drug in the treatment of CVC thrombosis. The KDOQI suggests that the success rate of rt-PA in restoring CVC patency is between 50% and 90% [1]. The most commonly used thrombolytic dose of alteplase is a 2 mg lumen. The minimum effective dose of alteplase is still unknown. Fink *et al.* [59] and Haymond *et al.* [60] reported that the 1.0 mg rt-PA dose may be as effective as the 2.0 mg dose in restoring CVC function. However, Yaseen *et al.* [61] observed that the clearance of catheter dysfunction by 2.0-mg rt-PA dwells was better than that by 1.0-mg rt-PA dwells, and the average survival life was improved. In addition, Savader *et al.* [62] and Davies *et al.* [63] found that the administration methods of the thrombolytic agent rt-PA mainly included push/withdrawal or dwell or thrombolytic agent (TLA) infusion in the treatment of CVC dysfunction, and these two techniques were equivalent to each other in restoring CVC function.

Reteplase (rPA) is a deletion mutant of rt-PA that can directly activate plasminogen without complexing with plasminogen [64]. Several studies conducted short dwell repeats of 0.4 U per catheter port for 30–60 min, and it was found that the success rate of relieving catheter dysfunction was approximately 85%–91%, which was equivalent to that of alteplase [65–67]. In addition, there was no significant difference in the patency rate improvement between the low-dose (0.5 U) reteplase and high-dose (2 or 3 U/lumen): 84% vs. 90% [68]. A systematic review compared thrombolytic drugs in patients with HD-occlusive CVC and found that the highest success rate of clearing catheter dysfunction was 88 ± 4%, followed by alteplase 81 ± 37% and tenecteplase (TNK) 41 ± 5% [69].

Tenecteplase (TNK) is a multipoint mutation of rt-PA that binds to fibrin and converts plasminogen into plasmin, thus stimulating local fibrinolysis [64]. Compared with the other plasminogen activators, the 1 h success rate of TNK (2 mg/mL) in the treatment of catheter dysfunction is approximately 22%–34%, and the long-term success rate can reach 49% [70,71]. Double-blind and placebo-controlled studies have evaluated non-HD patients with catheter failure treated with TNK and placebo (PBO), and the patients were assigned to two treatment arms (TNK-TNK-PBO and PBO-TNK-TNK). The initial 2 h success rates of catheter dysfunction were 60% and 23%, respectively; the cumulative restoration rates for CVC function increased to 87% after the second dose of TNK in both of the study arms combined [72]. It can be seen that TNK was efficacious for the restoration of catheter function, and prolonging its effect time can improve the success rate.

Urokinase-type plasminogen activator (u-PA) is a serine protease that binds to specific cell receptors (u-PARs), resulting in enhanced activation of cell-bound plasminogen [55] and it can dissolve fibrinogen and reduce the continuous formation of thrombosis. However, there is no consensus on its appropriate dose and use during treatment. Clase *et al.* [73] systematically reviewed several studies and concluded that the success rate of local catheter-guided u-PA 5000 IU in alleviating catheter obstruction was 74%–95%, while the success rate of systemic thrombosis with 250000 IU u-PA in completely improving blood flow was 81%–100%. Kumwenda *et al.* [74] used 12500–50000 IU or 100000–250000 IU u-PA infusion in patients with tunnel CVC dysfunction. The cumulative success rate of thrombolysis after the first intervention was 90.5%, 97% after the second intervention, and 99% after more than two interventions. There were no significant differences between the groups [74]. Compared with rt-PA and its derivatives, u-PA has no antithrombotic selectivity and reduces the thrombolytic fibrinolytic activity. A retrospective study and three RCT studies compared alteplase 1 mg/mL and u-PA 5000 IU/mL dwell for 30–120 min to improve catheter dysfunction. After comparing the success rate (defined by Qb $>$ 200 mL/min) of the restoration of catheter function of alteplase (88.2%–95%) vs. u-PA (42.8%–85%) [75–77], it was found that the success rate (defined by Qb $\geq$ 300 mL/min) of alteplase is twice that of u-PA (70.0% vs. 35%) [29].

Clinical recommendation

There are few studies on thrombolytic drugs as locking solutions, and the PreCLOT trial is the only one in which an ALS was able to reduce both catheter malfunction and CRBSI. The KDOQI suggests that rt-PA can be used prophylactically as a CVC lock solution once a week to help reduce CVC dysfunction [1]. However, with regard to CVC without thrombosis, evidence of the effect of the early use of rt-PA as a lock solution on the prevention of thrombosis is limited, which may lead to a waste of medical expenses. Therefore, rt-PA and its derivatives are suitable for patients with CVCs with confirmed or suspected thrombosis. Instead of a locking solution, KDOQI recommends the use of alteplase or urokinase plus citrate 4% per limb for restoring the intraluminal CVC blood flow in an occluded CVC [1].

Antibiotic lock solutions

Pros and cons of antibiotic lock solutions

Antibiotics combined with anticoagulants can effectively reduce CRBSI, but they can increase the risk of adverse drug reactions. Catheter thrombosis and CRBSI are interrelated, leading to catheter dysfunction. Theoretically, the antibiotic and anticoagulant locks can effectively prevent catheter dysfunction, but they also increases the risk of antibacterial toxicity and bacterial drug resistance.

Gentamicin + heparin/sodium citrate lock solution. Gentamicin is an aminoglycoside antibiotic that has efficacy against a broad bacteriological spectrum with the common bacteria in CRBSI. Dogra *et al.* [78] found that catheters locked with gentamycin-citrate (40 mg/mL with 3.13% citrate) performed better than those locked with heparin concerning CRBSI, but the difference in dysfunction was not significant. The measurable gentamicin level in some patients raised concerns about potential ototoxicity. Padilla-Orozco *et al.* [79] found that treatment with gentamicin (8 mg/mL and heparin 1000 U/mL lock solution) was associated with a significant decrease in CRBSI, especially with *Pseudomonas aeruginosa*. The other two studies confirmed that 5 mg/mL gentamicin combined with heparin as a lock solution could reduce the incidence and duration of CRBSI but had no significant effect on catheter function, and there was no bacterial drug resistance or clinical ototoxicity [80,81]. Nori *et al.* [82] confirmed that gentamicin (4 mg/mL)/citrate and minocycline/EDTA lock solutions were superior to heparin lock alone in the prevention of CRBSI, and the curative effect was equivalent to that of high concentration gentamicin. Nevertheless, Landry *et al.* [83] found that the incidence and mortality of gentamicin-resistant CRBSI were significantly higher in HD patients who were given gentamycin 4 mg/mL as a catheter lock within 6 months. To avoid drug resistance caused by the toxic accumulation of gentamicin, Moran *et al.* [84] and Moore *et al.* [85] combined 0.32 mg/mL gentamicin with citrate 4% as the sealing solution and found that a low concentration of gentamicin combined with citrate 4% could significantly reduce the rate of CRBSI without microorganisms developing resistance to gentamicin.

We pooled the results of the above studies, included all the patient groups together and found that compared with the heparin group, the incidence of CRBSI in both the low gentamicin concentration (0.32 mg/ml) and high gentamicin concentration ($>$4 mg/ml) groups was significantly lower than that in the heparin group (RR 0.19; 95% cl, 0.09–0.41; RR 0.26; 95% cl, 0.19–0.37, respectively). Therefore, considering the efficacy and safety, using low concentrations of gentamicin ($<$ 4 mg/mL) and low concentrations of citrate ($<$ 4%) as a lock solution can prevent and treat CRBSI. The low

concentration of gentamicin as a blocking solution did not increase the bacterial drug resistance, and the risk of drug toxicity was lower than that of the high concentration gentamicin.

Vancomycin + heparin/gentamicin locking solution. Vancomycin is a glycopeptide antibiotic with a narrow antibacterial spectrum. It is mainly used to treat methicillin-resistant infections, such as *Staphylococcus* spp. and *Enterococcus*. *In vitro* studies showed that the addition of 2500 U/mL heparin and 5 mg/mL vancomycin was effective in reducing the biofilm formation of *S. epidermidis*, *Enterococcus faecalis*, and *S. aureus* [86]. A randomized, double-blind, prospective study, including 131 hemodialysis patients with nontunnel catheters, showed that compared with heparin (2000 U/ml), vancomycin (5 mg/ml) combined with heparin (2000 U/ml) reduced the incidence of CRBSI by 82%, but during that period, vancomycin-resistant Enterococcus (VRE) was isolated from the vancomycin group, from which these patients had to be hospitalized [87]. A 12-month study confirmed that the combination of vancomycin (25 mg/mL) and gentamicin (40 mg/mL) could prevent *Staphylococcus* and other gram-negative bacterial infections in tunneled cuffed catheters (TCCs) and could significantly reduce the incidence of CRBSI and clinical sepsis; however, the exit infection rate was not significant [88]. We conducted pooled analyses that evaluated vancomycin-containing lock solutions versus heparin lock solutions and found that the incidence of CRBSI was 84% lower in the antibiotic group compared with the heparin group.

Cefazolin + gentamicin locking solution. Cefazolin is a broad-spectrum semisynthetic cephalosporin antibiotic that has good antibacterial activity against other G^+ and G^- bacilli, especially vancomycin-resistant enterococci, except methicillin-resistant *Staphylococcus*. Fogel *et al.* [89] found that cefazolin is equivalent to vancomycin and that the combination of cefazolin and gentamicin is better than vancomycin in stable outpatient HD patients with a low MRSA infection rate. Kim *et al.* [90] used the gentamicin (5 mg/mL) combined with cefazolin 10 mg/mL antibiotic lock technique (ALT) in 120 patients with nontunnelled central catheters and found that the CRBSI rate in the ALT group was significantly reduced compared with the non-ALT group. Moreover, in a study by Silva *et al.* [91], antibiotics (cefazolin 10 mg/mL) and lower concentrations of gentamicin (gentamicin 5 mg/mL) added to heparin (1000 U/mL) as a locking solution significantly reduced the incidence of CRBSI and extubation rate due to infection, and the difference in the amount of drug-resistant bacteria was not significant. Bueloni *et al.* [92] found that there was a difference between the gentamicin-cefazolin group and taurine-citrate group in the emergence of oxacillin-resistant strains but that there was no difference in CRBSI rates, which differs from the results of an analysis of these agents performed in a previous study by Silva. A meta-analysis including 5 trials of topical antibiotics (630 patients) and 11 trials of intraluminal antibiotics (765 patients) showed that prophylaxis with intraluminal agents significantly reduced the rate of catheter-related bloodstream infections (rate ratio, 0.32 (95% CI, 0.22–0.47); however, the reductions in the bacteremia rates remained significant for locks containing vancomycin and gentamicin but not for those containing cefazolin and gentamicin [93]. We conducted pooled analyses of cefazolin and gentamicin lock solutions versus heparin lock solutions and found that the incidence of CRBSI was 69% lower in the antibiotic group compared with the heparin group.

Other antibiotics + heparin

Cefotaxime + heparin locking solution. Cefotaxime is a third-generation semisynthetic cephalosporin that is not as effective as cefazolin against gram-positive bacteria but has strong activity against gram-negative bacteria. Saxena *et al.* [48,94,95] conducted three RCT studies on ESRD, diabetes, and elderly patients with nasal colonization by *S. aureus*. The studies confirmed that compared with the heparin group (5000 U/mL), the cefotaxime group (10 mg/mL) had improved thrombosis-free TCC survival at 365 days and infection-free survival but reductions in the incidence of CRBSI and the mortality of diabetes mellitus. However, further studies are needed to determine the long-term effects of antibiotic locking on drug resistance. Cefotaxime-heparin locking solutions can effectively reduce the incidence of gram-positive cocci (including MSSA)-related CRBSI when patients have nasal colonization by *S. aureus* [48,94,95].

Minocycline + EDTA locking solution. Minocycline is a semisynthetic tetracycline antibiotic with a wide antibacterial spectrum, and it can combine with tRNAs to achieve antibacterial effects. *S. aureus*, *Streptococcus*, *Escherichia coli*, and *P. aeruginosa* are sensitive to minocycline. Luiz *et al.* [96] found that compared with heparin 1000 IU/mL, minocycline 3 mg/mL with EDTA 30 mg/mL or 30% citrate as a lock solution could significantly reduce the incidence of CRBSI and improve the infection-free survival of catheters, but there was no significant difference between catheter survival and

dysfunction. Campos *et al.* [97] compared the effects of minocycline (3 mg/mL, EDTA (30 mg/mL), and conventional UFH on CRBSI in HD patients within 90 days. The results showed that the CRBSI-free survival rate in the minocycline EDTA group was significantly higher than that in the heparin group, but there was a significant difference in the catheter removal rate due to dysfunction [97].

Compound sulfamethoxazole + heparin locking solution. Sulfamethoxazole, a compound prepared from sulfamethoxazole and methoxy benzidine, mainly interferes with the synthesis of bacterial genetic material and exerts strong antibacterial activity, and it is used for *S. aureus*, *Klebsiella* spp., *E. coli*, and other drug-resistant bacteria. Moghaddas *et al.* [98] found that compared with heparin 2500 U/mL, compound sulfamethoxazole (10 mg/mL with heparin 2500 U/mL locking solution) reduced CRBSI and prolonged the survival time of CVCs in HD patients.

In this review, the pooled overall CVC-related bloodstream infection IRR, which was evaluated by including all the patient groups together and was used to compare the antibiotic locks with other lock solutions, showed that most IRRs per 1000 CVC-days were less than 1.00, suggesting a beneficial effect association with the antibiotic locks for the prevention of CVC-related bloodstream infections. Similarly, Labriola *et al.* [99] reviewed eight studies (829 patients, 882 catheters and 90191 catheter-days) and found that the use of antimicrobial lock solutions (ALS) significantly decreased the 68% incidence of CRBSI Additionally, in a systematic review of 11 trials assessing antibiotic catheter lock solutions (924 patients with 176,332 catheter-days) and 5 trials assessing 661 patients with 63,345 catheter-days, Yahav *et al.* [37] found that antibiotic catheter locks significantly reduced the catheter-related bloodstream infection rates by 56% and the catheter removal rates by 65%, as compared with heparin locks alone.

Clinical recommendation of antibiotic lock solutions

Gentamicin, vancomycin, and cefazolin are the most commonly used antibiotics for the prevention of CRBSI. However, there is insufficient evidence regarding adverse reactions and drug resistance in the use of cefotaxime, minocycline, and cotrimoxazole as locking solutions. Antibiotic locking solution can reduce the incidence of CRBSI, but due to the lack of anticoagulant properties, they need to be used in combination with heparin or citrate. The KDOQI guidelines recommend specific prophylactic antibiotic locks for patients in need of a long-term CVC at high risk of CRBSI, instead of using them for routine use.

Antimicrobial agents combined with anticoagulants

The use of antimicrobial agents combined with anticoagulants as locking solutions has been a research hotspot in recent years and can effectively reduce CRBSI, but there is no standard scheme.

Taurolidine

Taurolidine, a derivative of the amino acid taurine, is one of the latest ALTs and has broad-spectrum antibacterial activity against gram-positive and gram-negative bacteria and fungi (such as Candida) (including MRSA and VRE) by the binding of its hydroxymethyl group to cell walls, proteins, and cytotoxins [100]. Therefore, taurolidine can prevent the formation of biofilm in the catheter and reduce CRBSI. In recent years, in some European countries, a trisodium citrate 30% lock has been gradually replaced by the catheter locking solution containing taurolidine. At present, there are two commercial lock compound preparations, Taurolock™ (containing taurolidine and citrate 4%) and Neutrolin® (containing taurolidine, heparin, and calcium citrate).

The earliest research report on Taurolock™ that showed its association with increased frequency of catheter thrombosis versus heparin is attributed to Allon. This nonrandomized controlled study showed that although a significantly higher CRB-free survival at 90 days was observed with taurolidine/citrate than with heparin 5,000 U/ml (94 vs. 47%), almost 70% of the patients in the Taurolock™ group required thrombolytics to maintain catheter patency [101]. Betjes *et al.* [102] conducted an RCT test involving 58 patients, who mainly had nontunnel catheters (23.7%), and this study found that the antimicrobial taurolidine may significantly reduce the incidence of catheter-related sepsis but may not increase the risk of side effects. In a randomized controlled trial that included 119 chronic hemodialysis patients, Filiopoulos *et al.* [103] compared the antibiotic group(Gent 40 mg/ml + heparin 5000 u/ml, group A) and taurolidine/citrate group(group B), and found that the taurolidine/citrate lock was not superior to gentamicin/heparin in the prevention of CRB. Additionally, Solomon *et al.* [104] found that compared with heparin (5000 u/ml) in a randomized controlled trial, Taurolock™ did not reduce all-cause bacteremia and was associated with a greater need for thrombolytic therapy. However, the infection incidence caused by gram-negative bacteria decreased [104]. The pooled analyses of taurolidine/citrate lock solutions versus heparin lock solutions showed that the incidence of

CRBSI was decreased by 65%, but there was no significant changes in the catheter dysfunction incidence ($p = 0.69$).

To increase the antithrombotic effect, Solomon *et al.* [105] added 500 u/ml heparin to 4% taurine citrate, and TauroLock™-Hep500 (1.35% taurolidine, 4% citrate and 500 u/ml heparin) was compared to TauroLock™ (1.35% taurolidine, 4% citrate) and heparin 5000 u/ml by using retrospective data. Comparing with TauroLock™,TauroLock™ -Hep500 reduced the need for thrombolysis, which was equivalent to that of heparin 5000 u/ml, and the use of TauroLock™-Hep500 decreased the bacteremia rates from all causes by a factor of 2 [105]. An observational study showed that Neutrolin® was also able to reduce the incidence of CRBSI and catheter thrombosis [106]. The pooled analyses of all studies containing the TauroLock™-Hep500 lock solution showed that the patency of the catheter can be improved by 71% by adding heparin to taurolidine-citrate, but there was no significant difference in the incidence of CRBSI.

A prospective randomized controlled study confirmed that the twice a week TauroLock™-Hep500 (taurolidine-citrate-heparin 5000 U/mL) and weekly TauroLock™-U25,000 (taurolidine-citrate-urokinase 25000 IU) treatment schemes were very effective in preventing repeated thrombotic dysfunction of tunnel CVC catheters and significantly reduced the catheter replacement rate and the need for rt-PA emergency thrombolysis than TauroLock™-Hep500 after each HD session, but there was no significant difference in CRSBI [107]. Winnicki *et al.* [108] compared TauroLock™-U25,000U once a week with 4% citrate three times a week for high-risk HD patients with a history of multiple TD with incident catheters and found that the CRBSI rates in the TG was decreased by 75% compared to CG, and the catheter dysfunction incidence was 58% lower in the TG, which was significant. A prospective randomized study from Qatar investigated TaurolockHep500 and TauroLock™-U25,000 locks at the end of the third hemodialysis of the week in an unselected cohort (prevalent TCC accounted for 65%) and showed that TauroLock™-U25,000 could improve the catheter survival rate during the last dialysis [109]. Similarly, a cohort of TCC-TD high-risk patients or patients with a history of CRBSI in prevalent catheters showed that once a week rt-PA added to the citrate 4% lock solution significantly reduced the comprehensive outcome of catheter loss caused by thrombosis and infection [58]. We conducted a pooled analysis of the above studies by including all the studies' patient groups and found that taurolidine combined with citrate based locking solution can reduce the CRBSI rates by 66% and that the catheter failure incidence decreased by 53% in the hemodialysis patients with CVC after adding urokinase. (See, Tables 1 and 2)

Therefore, it is confirmed that the taurolidine/citrate combined preparation solution did work, but the effect of taurolidine lock alone is uncertain. In general, compared with heparin, the taurolidine/citrate locking solution can reduce the incidence of CRBSI, but it was not significant in improving catheter dysfunction. Adding heparin to the taurolidine/citrate locking solution can improve the patency of the catheter, but there was no significant difference in the incidence of CRBSI. However, the addition of urokinase to the taurolidine/citrate locking solution can reduce both the incidence of CRBSI and the incidence of catheter dysfunction.

Alcohol

Alcohol + heparin/4% sodium citrate combination.

Ethanol is an easily available and inexpensive fungicide that is widely used in clinics. It works by denaturing nonspecific proteins and usually does not produce bacterial resistance. *In vitro* studies confirmed that 70% ethanol was most effective against the common pathogens causing CRBSI [110]. Therefore, considering the toxicity and resistance of antibiotics, ethanol may be a promising alternative lock solution for the prevention of CRBSI in HD patients. Slobbe *et al.* [111] found that a 70% ethanol lock alone did not significantly reduce the incidence rate of CRBSI, and more preventive treatments were discontinued due to alcohol-related nonsevere adverse reactions. Vercaigne *et al.* [112] found that the 30% ethanol/4% sodium citrate lock reduced the incidence of catheter dysfunction and prolonged the survival time of catheters compared with heparin 1000 U/mL. In addition, the HEALTHY-CATH study confirmed that 70% ethanol once a week and 5000 U/mL heparin twice a week could reduce the infection rate compared with 5000 U/mL heparin three times a week; the catheter dysfunction and catheter-related blood infections were not significant [113]. Another prospective randomized study showed that 70% ethanol combined with heparin 2000 U/mL reduced the incidence of CRBSI compared with heparin 2000 U/mL, but there was no significant difference in the mean cumulative infection-free survival and thrombotic events [114]. Eventually, the pooled analyses of all the above studies, including ethanol-based lock solution, show that ethanol and anticoagulants can reduce the CRBSI rates by 57% but increase the catheter dysfunction incidence. There is no unified scheme for the appropriate

concentration of ethanol and the type and concentration of anticoagulants.

Hypertonic saline

It is well known that hypertonic saline has antibacterial effects. Oguzhan *et al.* [115] confirmed that the average catheter survival rate in 26% NaCl solution and heparin (1 mL 26% NaCl and 500 U/mL heparin in a 3 mL syringe) was significantly higher than that in 5000 U/mL heparin, but there was no significant difference in the CRBSI rate. A single-center RCT study from China found that for HD patients at a high risk of bleeding, the survival time of 10% NaCl catheter lock and dialysis blood flow were not significantly different from 3125 U/mL heparin. However, the incidence of catheter thrombosis and the need for u-PA treatment have increased significantly [116]. Considering that hypertonic saline can cause protein aggregation and increase the risk of thromboembolic diseases, there is still a lack of relevant research on the safety of hypertonic saline lock solutions. Therefore, hypertonic saline is not recommended as a conventional lock solution in the guidelines.

Sodium bicarbonate

Sodium bicarbonate-mediated calcium ion chelation indirectly inhibits the transformation of fibrinogen to fibrin, resulting in a decrease in coagulation function. Sodium bicarbonate has been proven to inhibit bacterial proliferation by reducing bacterial adhesion and preventing biofilm formation. A study conducted by a community hospital in the United States confirmed that sodium bicarbonate is safe as a lock solution and plays a better role than normal saline in preventing hemodialysis catheter removal caused by catheter thrombosis and CRBSI [117]. An RCT showed that the incidence of catheter removal due to thrombosis (CRT) in the sodium bicarbonate group was higher than that in the heparin group, whereas the incidence of CRBSI and ESI was lower in the sodium bicarbonate group. Sodium bicarbonate is considered an alternative catheter lock used in every HD session with rt-PA every 3 weeks, especially when heparin is prohibited [118].

However, Sayed *et al.* [119] compared the safety and efficacy of acute CVC using sodium a bicarbonate lock solution (SBCLS) versus an antibiotic catheter lock solution (ACLS) in the SBCLS (7.5% sodium bicarbonate) group and the ACLS (antibiotics + heparin) group. They found that there was no significant difference in catheter removal and catheter dysfunction caused by CRBSI between the two groups [119]. We conducted a pooled analyses of the sodium bicarbonate lock solution versus the control lock solution and found that the incidence of CRBSI decreased by 93%, but the catheter dysfunction incidence was increased by a factor of 6.03 (9.79% vs. 1.77%). In theory, sodium bicarbonate may be an alternative catheter lock solution because it has certain antibacterial and antithrombotic properties in theory. Due to the limited relevant research, the evidence is insufficient.

Summary

Based on the available evidence, we can conclude that:

1. the optimal composition of a lock is still matter of debate, and a low-dose heparin lock solution (such as 1000 U/mL) can efficiently achieve anticoagulation and will not increase the risk of bleeding. However, it does not completely eliminate the risk of HIT and promotes biofilm formation.
2. rt-PA and its derivatives can effectively prevent catheter dysfunction or diagnosed/suspected thrombosis in CVC, and no lock solution has demonstrated a benefit on catheter patency or catheter flow compared to heparin, excepted rt-PA.
3. there is no proof that citrate alone, even at high concentrations, is beneficial in comparison with heparin regarding CRBSI.
4. in theory, LMWH is not suitable as a lock solution.
5. there is a lack of unified formula composition and drug concentration of antibiotic/antimicrobial agents combined with an anticoagulant lock solution; therefore, a standard scheme needs to be established and further evaluated and verified. For patients at a high risk of suspected or confirmed CRBSI, the use of antibiotics and an anticoagulant lock solution is clinically beneficial.
6. there is a lack of follow-up validation data for LMWH, EDTA, taurolidine, sodium bicarbonate, ethanol, and other lock solutions.

In the future research on CVC lock solutions, patients with different thrombosis and infection risks should be stratified, and different lock solutions should be adopted for different patients. Thus, the indication and standardized formula of different CVC lock solutions should be established to maximize the curative effect and health economic benefits.

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