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Review

The efficacy of taurolidine containing lock solutions for the prevention of central-venous-catheter-related bloodstream infections: a systematic review and meta-analysis

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SUMMARY

The incidence of central venous catheter (CVC)-related bloodstream infections is high in patients requiring a long-term CVC. Therefore, infection prevention is of the utmost importance. The aim of this study was to provide an updated overview of randomized controlled trials (RCTs) comparing the efficacy of taurolidine containing lock solutions (TL) to other lock solutions for the prevention of CVC-related bloodstream infections in all patient populations. On 15th February 2021, PubMed, Embase and The Cochrane Library were searched for RCTs comparing the efficacy of TLs for the prevention of CVC-related bloodstream infections with other lock solutions. Exclusion criteria were non-RCTs, studies describing <10 patients and studies using TLs as treatment. Risk of bias was evaluated using the Cochrane Risk of Bias 2 tool. A random effects model was used to pool individual study incidence rate ratios (IRRs). Subgroup analyses were performed based on the following factors: CVC indication, comparator lock and bacterial isolates cultured. A total of 14 articles were included in the qualitative synthesis describing 1219 haemodialysis, total parenteral nutrition and oncology patients. The pooled IRR estimated for all patient groups together (nine studies; 918 patients) was 0.30 (95% confidence interval 0.19–0.46), favouring the TLs. Adverse events (10 studies; 867 patients) were mild and scarce. The quality of the evidence was limited due to a high risk of bias and indirectness of evidence. The use of TLs might be promising for the prevention of CVC-related bloodstream infections. Large-scale RCTs are needed to draw firm conclusions on the efficacy of TLs.

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Introduction

Central venous catheters (CVC) are essential for patients requiring long-term central venous access. CVCs, however, are associated with high rates of CVC-related bloodstream infections, which mainly depend on the patient group observed and CVC type inserted [1—3]. CVC-related bloodstream infections often result in hospital admissions for the administration of intravenous antibiotics, postponement of treatment for primary disease, early CVC removal, or intensive care unit admissions due to severe sepsis [4]. Prevention of CVC-related bloodstream infections is therefore of the utmost importance [5,6].

The use of prophylactic antimicrobial lock solutions with or without the addition of an anticoagulant have been suggested as a method for the prevention of CVC-related bloodstream infections by preventing biofilm formation, killing bacteria and/or the inhibition of bacterial growth. However, the efficacy of these antimicrobial lock solutions is still debated. Currently, in many hospitals, heparin-only lock solutions (HL) are used to maintain CVC patency. Heparin locks, however, do not have antimicrobial properties and current evidence suggests that regular saline locks might be as effective as heparin locks to maintain CVC patency [7—9]. A consensus meeting in 2016 reported that a lock solution containing taurolidine and/or citrate appears to be the most promising lock solution for the prevention of CVC-related bloodstream infections [9]. Taurolidine and citrate have antimicrobial, anti-biofilm and anticoagulant properties without reported antimicrobial resistance [9,10]. Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins and exotoxins, resulting in irreversible damage to the bacteria and inhibition of bacterial pathogenicity and surface adhesion of bacteria [11—14].

Currently, it is not yet clear how effective taurolidine-containing lock solutions (TLs) are for the prevention of CVC-related bloodstream infections and which patient populations are most likely to benefit from this lock solution [9]. Previous meta-analyses have been performed on this topic [15—20]. However, the majority of these meta-analyses did not include studies performed in all different patient groups. The most recent systematic review and meta-analysis including randomized controlled trials (RCTs) investigating the efficacy of TLs in all patient populations was published in 2014 [16]. Liu *et al*. included three RCTs and observed a possible beneficial effect of TLs for the prevention of CVC-related bloodstream infections. They concluded that further RCTs need to be performed to confirm the results [16]. We identified 11 additional articles published since then, or not included by Liu *et al*. [16]. Therefore, this systematic review and meta-analysis was conducted to give an updated overview of all the available evidence and draw more robust conclusions concerning the efficacy of TLs for the prevention of CVC-related bloodstream infections in several patient populations.

Methods

Search strategy and selection process

A systematic search in PubMed, The Cochrane Library and Embase was performed on 15 February 2021. All databases were searched from inception to 15 February 2021. Search strings were developed with the assistance of a medical librarian and contained terms and synonyms for taurolidine and infections (Appendix B). The systematic screening was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines of 2009 [21]. After removal of the duplicates, a title/abstract and full-text screening was performed independently by two authors (C.B., B.J.) using pre-defined in- and exclusion criteria. All original RCTs comparing the efficacy of TLs with any other lock solution for the prevention of CVC-related bloodstream infections in all patient populations were included. Exclusion criteria were non-RCTs, studies describing <10 patients and studies using TLs as treatment instead of prevention. The search was finalized by hand searches and snowballing. Disagreements were resolved by discussion (Figure 1).

Data collection process

Data from each study were extracted and double-checked by two authors (C.B., B.J.). Our primary outcome was the pooled incidence rate ratio (IRR) comparing the efficacy of TLs to non-antibiotic lock solutions in terms of the incidence rates (IRs) of CVC-related bloodstream infections per 1000 CVC-days. CVC-related bloodstream infection events were scored following the definitions stated in the original article, but must have at least included a positive blood culture in a patient with a CVC in situ.

Secondary outcomes were the incidence of adverse events (i.e. side-effects reported during lock replacement) and malfunction events (i.e. inability to flush and/or aspirate, thrombosis, administration of thrombolytics). Other data collected: first author, year of publication, study design, patient characteristics (number of patients included, CVC indication, age, in- or outpatient setting during CVC use, previous infections, and the administration of antibiotic prophylaxis), CVC characteristics (number of CVCs inserted, newly inserted CVCs, type, dwell time), lock characteristics (type, dose, frequency, method of removal), and CVC-related bloodstream infection characteristics (number of events following the definition reported in the article, CVC-related bloodstream infection definition and number of Gram-positive and Gram-negative bacteria cultured). In case of missing or unclear data, the authors were contacted by e-mail. If no response was obtained, the data was reported as missing.

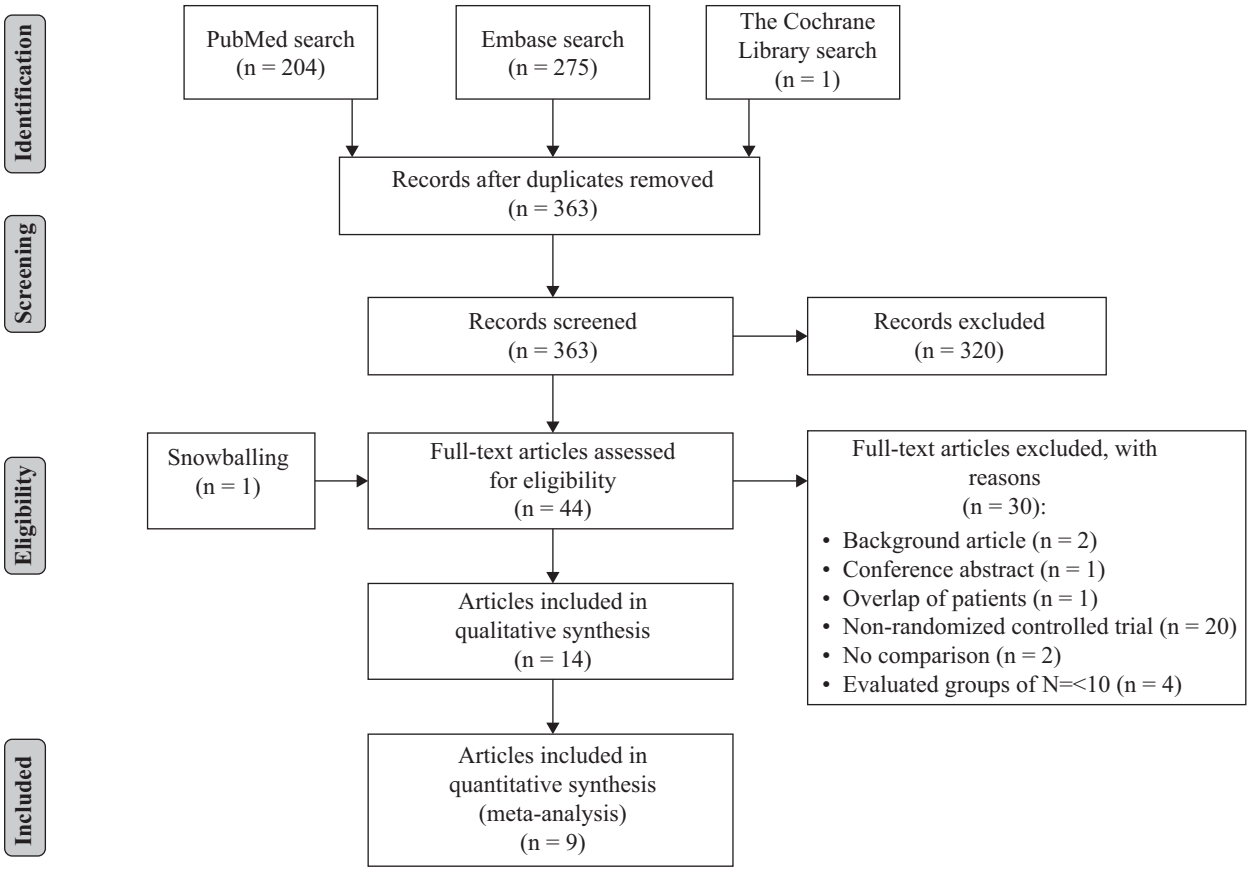

Figure 1. PRISMA Flow-diagram.

Risk of bias and applicability

The risk of bias per study was evaluated and double checked by two authors (C.B., B.J.) using the Risk of Bias (RoB) 2.0 tool for RCTs [22]. Additionally, the applicability of the included studies was assessed per PICOS (Population, Intervention, Comparator, Outcomes, and Setting) domain. Each domain was assessed for low (+), high (-), or moderate (±) applicability concerns [23].

Synthesis methods

The IRR along with the 95% confidence interval (CI) was used to compare the IRs of CVC-related bloodstream infections per 1000 CVC-days between the two study groups. If the IRR was not given, the IRR was estimated based on the total number of events and CVC-days reported. The exact confidence limits for the IRRs were computed based on the polynomial algorithm for person time data [24,25].

RCTs comparing TLs with other non-antibiotic locks were used in the meta-analyses using IRRs along with their 95% CIs. Additional meta-analyses were planned focusing on (1) the indication for CVC insertion (total parenteral nutrition (TPN), haemodialysis, oncology treatment), (2) the bacterial isolates cultured, (3) age per indication for CVC insertion (paediatrics and adults), and (4) the comparator lock used (i.e. HL, saline, citrate). A meta-analysis was performed if $\geq$3 studies could be included. Sensitivity analyses were performed excluding studies where (1) antibiotic prophylaxis use was reported by the authors, (2) citrate locks (CLs) (because citrate also has anti-biofilm properties) were used as a comparator, (3) non-tunnelled CVCs were included, and (4) only high-risk patients (i.e. history of $\geq$1 CVC-related bloodstream infections) were included in one or both groups. A random effects model was employed to pool the IRR in order to estimate an overall IRR and its 95% CI. An overall test on heterogeneity between the studies was performed for each meta-analysis (I^2). The heterogeneity was considered 'serious' if the I^2 was >50% and 'very serious' if the I^2 was >80%. Cochrane Review Manager Version 5.4 was used for the statistical analysis [26].

Reporting bias and quality of evidence assessment

To assess the presence of reporting bias, a funnel plot was used, where the estimate of the reported effect size was plotted against a measure of precision (standard error of log rate ratio). The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach for all outcomes and subgroup analyses performed [23].

Results

Study selection process

A total of 480 articles were identified from PubMed ($N = 204$), Embase ($N = 275$) and The Cochrane Library ($N = 1$). After duplicate removal, 363 articles were included for the

Table I
Study characteristics

	First author, year [Ref.]	Total *N* and population (in/out clinic)	CVC type	Study design	Patients (CVCs)		Age in years, mean or median* (SD or range)		Lock characteristics		
					TL group	Control group	TL group	Control group	TL group	Control group	Frequency and ml
HD	Winnicki, 2018 [68]	106 Adult (in)	Tunnelled	RCT Partially blind[a]	52 (52)	54 (54)	56 (15)	58 (15)	T1.35 C4 H500 (2x)/U25,000 (1x)	C4	2.3 mL 3×/week
	Zwiech, 2016 [70]	53 Adult (in)	(Non)-tunnelled	RCT Open	24 (24)	29 (29)	56 (12)	57 (15)	T1.35 C4 H500	H5000	CVC volume ± 0.1 mL after use
	Filiopoulos, 2011 [60]	119 Adult (in)	Non-tunnelled	RCT Open	59 (76)	60 (74)	75* (36–95)	72* (50–80)	T1.35 C4	G40 H5000	2.0 mL after use
	Solomon, 2010 [66]	107 Adult (in)	Tunnelled	RCT Double blind	53 (56)	54 (56)	60 (15)	57 (17)	T1.35 C4	H5000	CVC volume after use
	Betjes, 2004 [57]	58 Adult (in)	(Non)-tunnelled	RCT Open	– (37)	– (39)	58 (16)	50 (20)	T1.35 C4	H5000	CVC volume + 0.1 mL after use
Oncology	Gudiol, 2020 [61]	141 Adult[b] (in)	Non-tunnelled	RCT Double blind	72 (–)	69 (–)	56 * (–)	57 * (–)	T1.35 C4 H100	H1000	2.5 mL 3×/week
	Longo, 2017 [64]	160 Adult (in/out)	VAP	RCT Open	84 (84)	76 (76)	62 (54–70)	61 (53–69)	T1.35 C4	S0.9	3.0 mL after use
	Handrup, 2013 [62]	112 Paediatric (in)	Tunnelled, VAP	RCT Open	58 (64)	54 (65)	6 * (0–19)	5 * (0–16)	T1.35 C4 H100	H250	2.5 mL after use
	Dümichen, 2012 [59]	71 Paediatric (in)	Tunnelled	RCT Open	35 (35)	36 (36)	9 * (8)	8 * (6)	T1.35 C4	H100	CVC volume after use
TPN	Wouters, 2018 [69]	105 Adult (out)	(Non)-tunnelled, VAP	RCT Double blind	53 (53)	52 (52)	59–47 * (–)[c]	55–47 * (–)[c]	T2	S0.9	5.0 mL 2–7×/week
	Tribler, 2017 [67]	41 Adult (out)	Tunnelled	RCT Double blind	20 (20)	21 (21)	56 (13)	58 (12)	T1.35 C4 H100	H100	2.0–4.0 mL 2–7x/week
	Klek, 2015 [63]	30 Adult (out)	Tunnelled	RCT Open	10 (10) and 10 (10)	10 (10)	44 (–) and 46 (–)	46 (–)	T2 and T1.35 C4	S0.9	-mL after use
	Bisseling, 2010 [58]	30 Adult (out)	Tunnelled, VAP	RCT Open	16 (16)	14 (14)	55 (13)	49 (16)	T2	H150	5.0 mL –
Other	Łyszkowska, 2019 [65]	86 Paediatrics <2 years old undergoing surgery (in)	(Non)-tunnelled	RCT Open	– (48)	– (49)	– (–)	– (–)	T- C-	–	2.0 mL after use

-, missing; C, citrate; CO, cross-over; CVC, central venous catheter; G, gentamicin mg/mL; H, heparin IU/mL; HD, haemodialysis; NA; not applicable; PC, prospective cohort study; RC, retrospective cohort study; RCT, randomized controlled trial; SD, standard deviation; SL; saline %; T; taurolidine %; TL, taurolidine lock; TPN, total parenteral nutrition; U, urokinase IU/mL; VAP, vascular access port.

[a] Partially blinded: blinding of patients, laboratory staff, and assessors. Nurses and physicians were not blinded.

[b] Only patients in neutropenia.

[c] Patients were divided into a new CVC/pre-existing CVC group for the baseline characteristics.

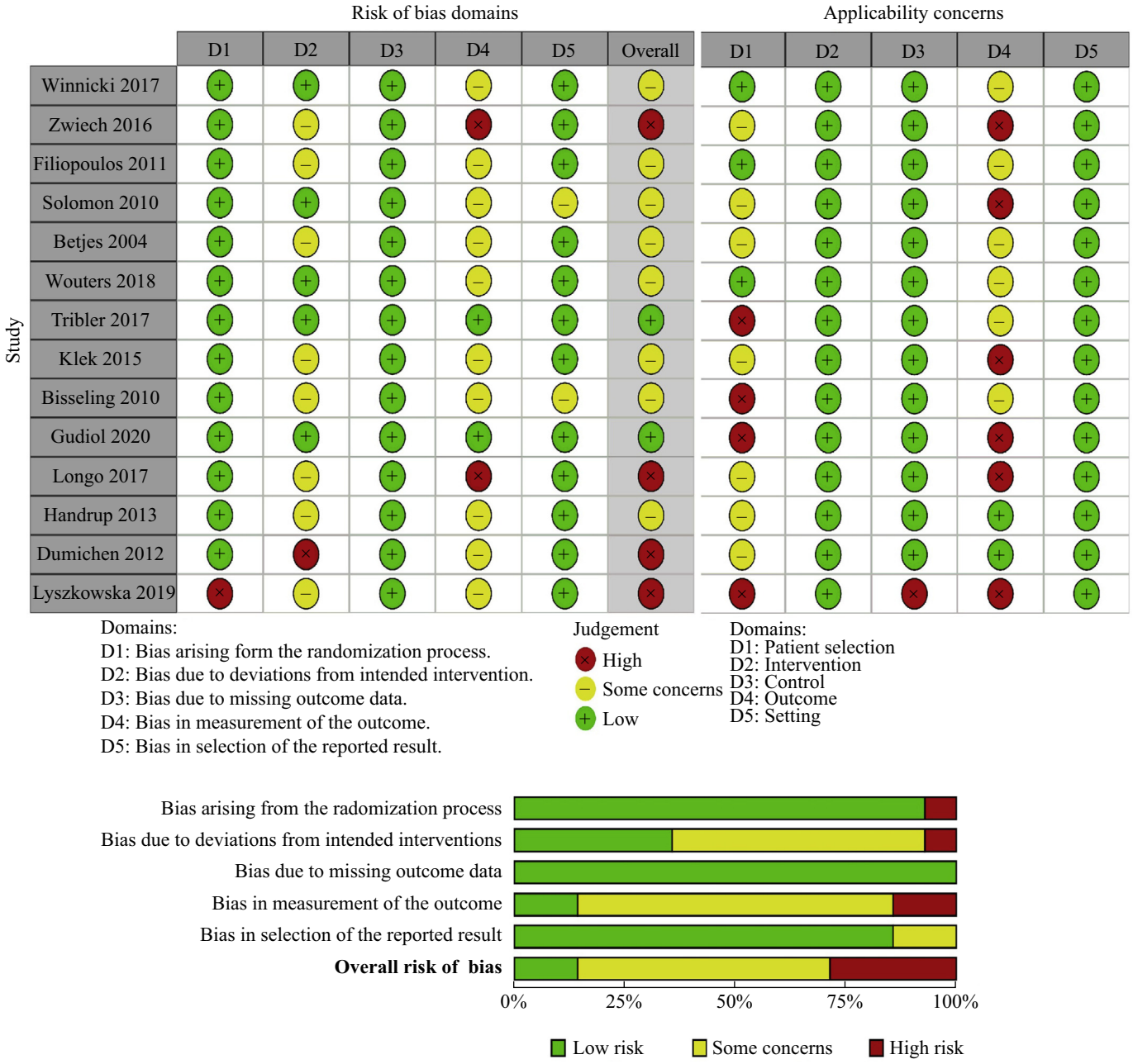

Figure 2. Risk of bias (RoB 2.0) evaluation and applicability concerns of randomized controlled trials.

title and abstract screening. Three conflicts were observed afterwards, which were resolved by discussion. A total of 44 articles were eventually included in the full-text screening, of which one article was added after snowballing. Thirty articles were excluded after full-text screening [27–56]. Fourteen articles (1219 patients) were included in the qualitative synthesis, nine (918 patients) of these articles were included in the quantitative synthesis [57–70] (Figure 1).

Study characteristics

Of the 14 included articles, five (36%) had a blinded study design, of which four had a double-blinded design [61,66–69]. Two (14%) non-blinded studies used an assessor-masked design to avoid bias [62,64]. The 14 included articles described patients receiving haemodialysis ($N = 5$, 36%) or TPN ($N = 4$, 29%), oncology patients ($N = 4$, 29%), or a combination of these ($N = 1$, 7%). The majority, described patients with tunnelled CVCs and/or vascular access ports (VAPs) ($N = 12$, 86%). A small number of articles discussed also or only patients with non-tunnelled CVCs ($N = 6$, 43%).

In three (21%) studies, the use of prophylactic antibiotics during the study period was reported; cotrimoxazole for the prevention of *Pneumocystis jirovecii* pneumonia [59], nasal mupirocin ointment before CVC insertion for the prevention of *Staphylococcus aureus* infections [68], and systemic antibiotic prophylaxis not further specified [61].

Most studies compared TLs with or without the addition of heparin and/or citrate to regular saline or heparin locks ($N = 12$, 86%), and one study used CLs as a comparator. Another

Table II
Study outcomes

	First author, year [Ref.]	Study design (*N*)	Lock type		Infection events, total (GP/GN isolates[d])		CVC-days		CVC-related bloodstream infection IR per 1000 CVC-days		CVC-related bloodstream infection IRR per 1.000 CVC days (CI), *P*-value	CVC-related bloodstream infection definition
			TL	Control	TL	Control	TL	Control	TL	Control		
HD	Winnicki, 2018 [68]	RCT Partially blind[a] (106)	TCHL/UL	CL	6 (4/4)	18 (5/19)	8982	6708	0.67	2.68	0.25 (0.09–0.63), <0.01	Symptoms, CVC BC+, no other source OR defervescence after removal
	Zwiech, 2016 [70]	RCT Open (53)	TCHL	HL	0 (0/0)	26 (26/0)	–	7558[c]	0.00	3.44	NA	Routine BC+
	Filiopoulos, 2011 [60]	RCT Open (119)	TCL	GHL	8 (8/0)	6 (3/3)	2180[c]	2190[c]	3.67	2.74	1.34[c] (0.47–3.86), 0.78[c]	Symptoms, CVC BC+, no other source
	Solomon, 2010 [66]	RCT Double blind (107)	TCL	HL	11 (10/2)	23 (12/12)	8129	9642	1.35	2.39	0.57[c] (0.28–1.16), 0.16[c]	Symptoms, CVC BC+
	Betjes, 2004 [57]	RCT Open (58)	TCL	HL	0 (0/0)	4 (4/0)	1519	1885	0.00	2.12	NA	Symptoms, CVC BC+, no other source
Oncology	Gudiol 2020 [61]	RCT Double blind (141)	TCHL	HL	2 (2/0)	1 (1/0)	719[c]	690[c]	2.78	1.45	1.92 (0.18–20.66), 1.00[c]	Symptoms, peripheral BC+ (2 × BC+ for commensals), no other source.
	Longo, 2017 [64]	RCT Open (160)	TCL	SL	1 (1/0)	4 (4/0)	10,000[c]	10,000[c]	0.1	0.4	0.23 (0.03–2.06), 0.21	Peripheral BC+ with same organism as exudate/CVC segment/BC with differential time to positivity difference of >2 h.
	Handrup, 2013 [62]	RCT Open (112)	TCHL	HL	7 (5/4)	26 (13/11)	17,500[c]	18,571[c]	0.4	1.4	0.26 (0.09–0.61), <0.01	CVC BC+ >2 h before peripheral BC+. If no peripheral BC available: symptoms, BC+(2 × BC+ for commensals), no other source.
	Dümichen, 2012 [59]	RCT Open (71)	TCL	HL	2 (–/–)	9 (–/–)	6576	7233	0.30	1.24[b]	0.24[c] (0.05–1.13), 0.09[c]	Symptoms, BC+ (2 × BC+ for commensals), no other source

TPN	Wouters, 2018 [69]	RCT Double blind (105)	TL	SL	5 (4/1)	18 (7/10)	15,318	12,493	0.33	1.44	0.23 (0.07−0.63), <0.01	Symptoms, CVC BC+ (2 × BC+ for commensals), no other source
	Tribler, 2017 [67]	RCT Double blind (41)	TCHL	HL	0 (0/0)	7 (4/2)	9622	6956	0.00	1.01	NA	Symptoms, CVC BC+, no other source
	Klek, 2015 [63]	RCT Open (30)	TL; TCL	SL	0 (0/0); 1 (0/1)	0 (0/0)	3658; 3650	3660	0.00; 0.27	0.00	NA	Symptoms, BC+
	Bisseling, 2010 [58]	RCT Open (30)	TL	HL	1 (0/0)	10 (7/3)	5370	4939	0.19	2.02	0.09[c] (0.01−0.72), <0.01[c]	Symptoms, 2 × BC+, no other source
Other	Łyszkowska, 2019 [65]	RCT Open (86)	TCL	−	1 (1/0)	14 (12/2)	942	976	1.06	14.34	0.07[c] (0.01−0.56), <0.01[c]	Symptoms, BC+

-, missing; BC, blood culture; CI, confidence interval; CO, cross-over study; CVC, central venous catheter; GHL, gentamicin heparin lock; GN, Gram-negative; GP, Gram-positive; HD, haemodialysis; HL, heparin lock; IR, incidence rate; IRR, incidence rate ratio; NA, not applicable; PC, prospective cohort study; RC, retrospective cohort study; RCT, randomized controlled trial; SL, saline lock; TCHL, taurolidine citrate heparin lock; TCL, taurolidine citrate lock; TL, taurolidine lock; TPN, total parenteral nutrition; UL, urokinase lock.

[a] Partially blinded: blinding of patients, laboratory staff, and assessors. Nurses and physicians were not blinded.

[b] The authors describe a different incidence rate of 1.3 for the control group which we cannot trace back to the data described in the article.

[c] Estimated by hand because no IRR and/or CVC-days were given in the article.

[d] The total number of GP/GN isolates can be less than the total number of infections since yeast and fungi infections are not reported here, and might also be higher since the isolates of combined GP and GN infection episodes were reported separately.

Table III
Adverse events

	First author, year [Ref.]	TL lock (total number of patients)	Control lock (total number of patients)	TL aspirated	TL group adverse events (number of patients)	Control lock aspirated	Control group adverse events (number of patients)
HD	Filiopoulos, 2011 [60]	T1.35 C4 (59)	G40 H5000 (60)	Yes	0	Yes	0
	Betjes, 2004 [57]	T1.35 C4 (X)	H5000 (X)	Yes	0	Yes	0
Oncology	Gudiol, 2020 [61]	T1.35 C4 H100 (72)	H1000 (69)	Yes	0	Yes	0
	Longo, 2017 [64]	T1.35 C4 (84)	S0.9 (76)	Yes	Local paresthesia (9), body warm sensation (4), unpleasant taste (1), pain (1)	No	—
	Handrup, 2013 [62]	T1.35 C4 H100 (58)	H250 (54)	—	Unpleasant taste (-)	—	0
	Dümichen, 2012 [59]	T1.35 C4 (35)	H100 (36)	Yes	Discomfort chest/neck (1), perioral dysesthesia (1), unpleasant taste (2), nausea (2), vomiting (1)	Yes	0
TPN	Wouters, 2018 [69]	T2 (53)	S0.9 (52)	—	Unpleasant taste (1), dizziness (1), erhythema exit-site (1)	—	Flushing (1)
	Tribler, 2017 [67]	T1.35 C4 H100 (20)	H100 (21)	No	Unpleasant taste (8), paresthesia (3), nausea/ vomiting (2)	No	Heartburn/acid reflux (1), paresthesia (1), dizziness (1)
	Klek, 2015 [63]	T2 (10)	S0.9 (10)	No	0	No	0
		T1.35 C4 (10)	"	No	0	No	"
	Bisseling, 2010 [58]	T2 (16)	H150 (14)	—	0	—	0

-, missing; C, citrate %; CO, cross-over study; G, gentamicin mg/mL; H, heparin IU/mL, HD, haemodialysis; PC; prospective cohort study; RC, retrospective cohort study; RCT, randomized controlled trial; S, saline %; T, taurolidine %' TL, taurolidine lock.
TPN, total parenteral nutrition.

Table IV
Forest plot summary table

Population	Primary or sensitivity analyses	Studies	Studies/outcomes included in the analysis	IRR (95%CI)	I^2, *P*-value
All patients	Primary analyses	9	All RCTs	0.30 (0.19–0.46)	14%, <0.01
		7	Only Gram-positive CVC infections as outcome	0.63 (0.38–1.02)	0%, 0.06
		4	Only Gram-negative CVC infections as outcome	0.21 (0.11–0.40)	0%, <0.01
		5	All RCTs comparing TLs with a heparin-only lock solution	0.36 (0.18–0.71)	33%, <0.01
	Sensitivity analyses	6	Excluding RCTs with antibiotic prophylaxis	0.28 (0.16–0.49)	26%, <0.01
		8	Excluding RCTs with citrate locks as comparator	0.30 (0.18–0.50)	23%, <0.01
		6	Excluding RCTs with non-tunnelled CVCs	0.33 (0.21–0.50)	0%, <0.01
		8	Excluding RCTs with only high-risk patients	0.31 (0.20–0.48)	11%, <0.01
Oncology patients	Primary analyses	4	All RCTs	0.30 (0.15–0.59)	0%, <0.01
	Sensitivity analyses	3	Excluding RCTs with non-tunnelled CVCs	0.25 (0.12–0.51)	0%, <0.01

CI, confidence interval; CVC, central venous catheter; IRR, incidence rate ratio; RCT, randomized controlled trial; TL, taurolidine-containing lock solution.

study used gentamicin locks as a comparator, this study was therefore not included in the meta-analyses (Table I).

Risk of bias and applicability

A 'moderate' to 'high' risk of bias was observed in a majority of the studies, mainly due to open-labelled study designs, inappropriate definitions of CVC-related bloodstream infections and/or confounding factors (Figure 2).

The applicability per evaluated domain was scored as 'moderate' or 'high' concerns for some studies, because patients with previous CVC-related bloodstream infections or not newly inserted CVCs were included, the comparator lock was not described, and/or the CVC-related infection definition was inappropriate (Figure 2).

Results of individual studies

Many studies observed an IRR per 1000 CVC-days of less than 1.00, suggesting a beneficial effect associated with the TLs compared with other lock solutions for the prevention of CVC-related bloodstream infections. Two studies reported an IRR of more than 1.00, both with *P*-values of >0.05 [60,61]. For four (28.6%) studies, the IRR could not be estimated because in one of the groups no events occured [57,63,67,70] (Table II).

A total of 867 patients (417 in the TL group and 392 in the control group, one study did not report the number of patients per group) were followed up to observe the occurrence of adverse events. In the TL group, the most frequently reported adverse events were: paraesthesia ($N = 13$, 3.1%), unpleasant taste ($N = 12$, 2.9%), and nausea/vomiting ($N = 5$, 1.2%). In the control group, four patients reported adverse events (Table III).

A significant difference between the groups regarding the IRs of malfunctions and/or administration of thrombolysis was observed by two RCTs, one favouring the TL group [68] and one favouring the control group [66] (see Supplementary Table S1).

Results of syntheses

The pooled overall CVC-related bloodstream infection IRR including all patient groups together comparing TLs with non-antibiotic locks was 0.30 (0.19–0.46 95% CI), favouring the TL. Subgroup analyses showed IRRs of 0.63 (0.38–1.02 95% CI) for Gram-positive bloodstream infections (Gram-positive prophylaxis was reported by three studies), and 0.21 (0.11–0.40 95% CI) for Gram-negative bloodstream infections (Gram-negative prophylaxis use was not reported by these studies). Further subgroup analyses showed IRRs of 0.36 (0.18–0.71 95% CI) for studies with a HL as comparator, and 0.30 (0.15–0.59 95% CI) for studies including oncology patients only, all favouring the TL. Not enough RCTs were identified to perform analyses for haemodialysis and TPN patients, paediatric and adult patients per CVC indication, and other comparator lock solutions (i.e. saline and citrate). Sensitivity analyses showed no major differences in the pooled IRR compared with the primary analyses (Table IV or see Supplementary Figures S1 and S2).

Reporting bias and quality of evidence assessment

The quality of evidence was reduced from 'high' to 'moderate' or 'low' due to a high risk of bias and indirectness of evidence. After evaluation of the funnel plots, reporting bias was not suspected (see Supplementary Table S2 and Supplementary Figure S3).

Discussion

This comprehensive review and meta-analysis suggests that the use of TLs is promising and safe for the prevention of CVC-related bloodstream infections. Adverse events observed were all mild and scarce. The quality of evidence however, is not yet high due to a high risk of bias and indirectness of evidence observed, as described in more detail below. These results are in accordance with previously performed reviews and meta-analyses [15–19,71–75].

The outcomes of the subgroup analyses for Gram-positive and Gram-negative isolates suggest that TLs may be more

effective against Gram-negative compared with Gram-positive bacteria, as also reported by previous authors [17,60,66,68]. *In vitro* studies, however, did not show this difference in effect [10,11]. This finding, might be explained by the limitations of the CVC-related bloodstream infections definitions used, resulting in the registration of positive blood cultures as a CVC-related bloodstream infection instead of colonization, contamination or a non-CVC-related bloodstream infection [2,76].

Strengths of this review and meta-analysis are that it provides an updated summary of the available evidence regarding the efficacy of TLs, that data on all possible confounders are collected, and that subgroup and sensitivity analyses are performed. In addition, it underlines the importance of further qualitative research in larger populations with the aim of significantly reducing the high IR of CVC-related bloodstream infections. We identified several aspects that are important for future research and the correct interpretation of the results from CVC lock studies, that were not always taken into account in the included studies.

Future RCTs should ideally be double-blind or at least assessor-masked. Only a small number of studies used a double-blinded design and two non-blinded studies used an assessor-masked design to avoid bias [61,62,64,66–69]. Furthermore, the CVC-related bloodstream infection definition should be clear and at least include clinical symptoms and a positive blood culture, exclude other sources of infections, and ideally use the central line-associated bloodstream infection (CLABSI) or catheter-related bloodstream infection (CRBSI) definition [2,76]. This was done by 10 (71.4%) of the included studies [57–62,64,67–69]. Additionally, confounding factors, such as diagnosis, CVC type, CVC insertion days, antibiotic prophylaxis and TPN administration, CVCs that were already *in situ* at the beginning of the study, previous CVC-related infections, lock dwell time and lock frequency should be equally distributed between the intervention groups [2,9]. Most of these factors were not taken into account in many of the included studies.

Indirectness of evidence was also suspected. First, due to the inclusion of studies including only high risk patients (i.e. patients with a history of CVC-related bloodstream infections), resulting in the use of TLs as secondary instead of primary prophylaxis [58]. Second, due to the use of inappropriate (i.e. not following the minimal requirements as described above) CVC-related bloodstream infection definitions [63,65,66,70].

We did not observe a high heterogeneity between the studies (i.e. I^2 values $<50\%$). However, the minimal heterogeneity that was observed, could be explained by the differences between the study populations included, CVC types inserted, lock solutions and protocols used, and outcome measures observed [2,3]. Gudiol *et al.* (2020) reported an IRR of >1.00. This might be explained by the inclusion of only non-tunnelled CVCs. The sensitivity analysis excluding RCTs with non-tunnelled CVCs also showed a much lower I^2 value compared with the primary meta-analysis. Other additional and sensitivity meta-analyses performed suggested no major differences in the effect of TLs against CVC-related bloodstream infections [61].

Filiopoulos *et al.* (2011) used a gentamicin lock instead of a non-antibiotic lock as a comparator and was therefore excluded from the meta-analysis. They reported an IRR of >1.00, $P > 0.05$. This might suggest a similar or even superior efficacy of gentamicin locks compared with TLs [60]. Compared with TLs, however, gentamicin and other antibiotic locks might increase the risk of microbial resistance and the use of these locks is therefore not preferred. Microbial resistance to taurolidine has not been observed [9,10].

Limitations of this review are that not all articles could be included in the meta-analysis because the IRRs along with their 95% CIs were not given or could not be estimated due to data not reported in the article or the presence of zero events. Additionally, not enough RCTs were identified to perform analyses for haemodialysis, TPN and paediatric patients separately. The efficacy of TL might differ between these populations due to the differences in the aetiology and primary risk of CVC-related bloodstream infections between these groups caused by the underlying disease, treatments received, and CVC protocols used (e.g., high-risk chemotherapy, TPN, antibiotic prophylaxis, total CVC insertion days, CVC types and lock frequency) [2,3].

Large-scale RCTs for each patient population, including cost-effectiveness analyses, are required to draw more robust conclusions on the efficacy of TLs for the prevention of CVC-related bloodstream infections. Additionally, further research is required to provide information about the efficacy of TLs for the prevention of Gram-positive CVC-related bloodstream infections.

In conclusion, the results of this review and meta-analysis suggest that the use of TLs for the prevention of CVC-related bloodstream infections is promising. The quality of the evidence was limited due to a high risk of bias and indirectness of evidence, mainly due to the presence of non-blinded study designs, confounding factors and a wide heterogeneity in populations observed and outcome definitions used. In the future, large blinded RCTs, including cost-effectiveness analyses, should be performed investigating the efficacy of TLs for the primary prevention of CVC-related bloodstream infections in different patient groups and the efficacy of TLs against Gram-positive CVC-related bloodstream infections specifically.

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Author contributions

Methodology: M.vdW., A.S., M.W., M.F., B.J. and C.B. Investigation: B.J. and C.B. Formal analysis: M.F., B.J. and C.B. Writing – original draft: C.B. and B.J. Writing –Review and Editing: M.vdW., A.S., M.W., M.F., F.F., T.B., Y.L., C.V., B.J. and C.B. Supervision: M.vdW., A.S., M.F., M.W.

Conflict of interest statement

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.10.022.

Appendix B. Search string

PubMed (N = 204)

("taurolidine" [Supplementary Concept] OR Taurolidin* [tiab] OR Tauroflex*[tiab] OR Taurolin*[tiab] OR Taurolock* [tiab]) AND ("Infections" [Mesh] OR Infection*[tiab] OR Infected*[tiab] OR Infestation*[tiab] OR Infectious*[tiab] OR Sepsis* [tiab] OR Septicemia*[tiab] OR Blood Poisoning*[tiab] OR Bacteremia*[tiab] OR Fungemia*[tiab] OR Mycoses*[tiab] OR CRBSI* [tiab] OR CLABSI*[tiab]).

Embase (N = 275)

Filters: Article; Article in press; Review; ('taurolidine'/exp OR 'taurolidin*':ti,ab,kw OR 'tauroflex*':ti,ab,kw OR 'taurolin*':ti,ab,kw OR 'taurolock*':ti,ab,kw) AND ('infection'/exp OR 'infection*':ti,ab,kw OR 'infected*':ti,ab,kw OR 'infestation*':ti,ab,kw OR 'infectious*':ti,ab,kw OR 'sepsis*':ti,ab,kw OR 'septicemia*':ti,ab,kw OR 'blood poisoning*':ti,ab,kw OR 'bacteremia*':ti,ab,kw OR 'fungemia*':ti,ab,kw OR 'mycoses*':ti,ab,kw OR 'CRBSI*':ti,ab,kw OR 'CLABSI*':ti,ab,kw).

Cochrane (N = 1)

(taurolidin*:ti,ab,kw OR tauroflex*:ti,ab,kw OR taurolin*':ti,ab,kw OR taurolock*:ti,ab,kw) AND (infection*:ti,ab,kw OR infected*:ti,ab,kw OR infestation*:ti,ab,kw OR infectious*:ti,ab,kw OR sepsis*:ti,ab,kw OR septicemia*:ti,ab,kw OR blood poisoning*:ti,ab,kw OR bacteremia*:ti,ab,kw OR fungemia*:ti,ab,kw OR mycoses*:ti,ab,kw OR CRBSI*:ti,ab,kw OR CLABSI*:ti,ab,kw).

Total (N = 480)

After duplicate removal N = 363.

References

[1] Schoot RA, van Dalen EC, van Ommen CH, van de Wetering MD. Antibiotic and other lock treatments for tunnelled central venous catheter-related infections in children with cancer. Cochrane Database Syst Rev 2013;6:CD008975.

[2] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49(1):1–45.

[3] de Jonge RC, Polderman KH, Gemke RJ. Central venous catheter use in the pediatric patient: mechanical and infectious complications. Pediatr Crit Care Med 2005;6(3):329–39.

[4] van den Bosch CH, van der Bruggen JT, Frakking FNJ, Terwisscha van Scheltinga CEJ, van de Ven CP, van Grotel M, et al. Incidence, severity and outcome of central line related complications in pediatric oncology patients; a single center study. J Pediatr Surg 2019;54(9):1894–900.

[5] Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(Suppl 2):S89–107.

[6] O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention, U.S. Pediatrics 2002;110(5):e51.

[7] Bradford NK, Edwards RM, Chan RJ. Normal saline (0.9% sodium chloride) versus heparin intermittent flushing for the prevention of occlusion in long-term central venous catheters in infants and children. Cochrane Database Syst Rev 2020;4:CD010996.

[8] Lopez-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults. Cochrane Database Syst Rev 2018;7:CD008462.

[9] Pittiruti M, Bertoglio S, Scoppettuolo G, Biffi R, Lamperti M, Dal Molin A, et al. Evidence-based criteria for the choice and the clinical use of the most appropriate lock solutions for central venous catheters (Excluding dialysis catheters): a GAVeCeLT consensus. J Vasc Access 2016;17(6):453–64.

[10] Olthof ED, Rentenaar RJ, Rijs AJ, Wanten GJ. Absence of microbial adaptation to taurolidine in patients on home parenteral nutrition who develop catheter related bloodstream infections and use taurolidine locks. Clin Nutr 2013;32(4):538–42.

[11] Olthof ED, Nijland R, Gulich AF, Wanten GJ. Microbiocidal effects of various taurolidine containing catheter lock solutions. Clin Nutr 2015;34(2):309–14.

[12] Caruso F, Darnowski JW, Opazo C, Goldberg A, Kishore N, Agoston ES, et al. Taurolidine antiadhesive properties on interaction with E. coli; Its transformation in biological environment and interaction with bacteria cell wall. PLoS One 2010;5:e8927.

[13] Gorman SP, McCafferty DF, Woolfson AD, Jones DS. Reduced adherence of micro-organisms to human mucosal epithelial cells following treatment with Taurolin, a novel antimicrobial agent. J Appl Bacteriol 1987;62(4):315–20.

[14] Gorman SP, McCafferty DF, Woolfson AD, Jones DS. Electron and light microscopic observations of bacterial cell surface effects due to taurolidine treatment. Lett Appl Microbiol 1987;4(5):103–9.

[15] Kavosi Z, Sarikhani Khorrami M, Keshavarz K, Jafari A, Hashemi Meshkini A, Safaei HR, et al. Is taurolidine-citrate an effective and cost-effective hemodialysis catheter lock solution? A systematic review and cost- effectiveness analysis. Med J Islam Repub Iran 2016;30:347.

[16] Liu H, Liu H, Deng J, Chen L, Yuan L, Wu Y. Preventing catheter-related bacteremia with taurolidine-citrate catheter locks: a systematic review and meta-analysis. Blood Purif 2014;37(3):179–87.

[17] Liu Y, Zhang AQ, Cao L, Xia HT, Ma JJ. Taurolidine lock solutions for the prevention of catheter-related bloodstream infections: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2013;8(11):e79417.

[18] Sun Y, Wan G, Liang L. Taurolidine lock solution for catheter-related bloodstream infections in pediatric patients: a meta-analysis. PLoS One 2020;15(4):e0231110.

[19] van de Wetering MD, van Woensel JB, Lawrie TA. Prophylactic antibiotics for preventing Gram positive infections associated with long-term central venous catheters in oncology patients. Cochrane Database Syst Rev 2013;11:CD003295.

[20] Wouters Y, Causevic E, Klek S, Groenewoud H, Wanten GJA. Use of catheter lock solutions in patients receiving home parenteral nutrition: a systematic review and individual-patient data meta-analysis. JPEN J Parenter Enteral Nutr 2020;44:1198–209.

[21] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.

[22] Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

[23] Schünemann H. BJ, Guyatt G., Oxman A., editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group Updated October 2013. Available at: guidelinedevelopment.org/handbook [last accessed September 2021].

[24] Martin DAH. An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. Epidemiology 1991;2:359—62.
[25] Martin DAH. Exact estimates for a rate ratio. Epidemiology 1996;7:29—33.
[26] Review Manager Web (RevMan Web). Released 09-2020. Version 5.4. 1 ed. The Cochrane Collaboration; 2020. Available at: revman.cochrane.org [last accessed October 2021].
[27] Akyuz CKS, Yagci-Kupeli B, Buyukpamukcu M. Prophylactic taurolidine use in central venous catheters of pediatric cancer patients: a prospective randomized study from single center. Pediatric Blood and Cancer 2010;42. Congress of the International Society of Pediatric Oncology, SIOP 2010, Boston, MA United States.
[28] Al-Amin AH, Sarveswaran J, Wood JM, Burke DA, Donnellan CF. Efficacy of taurolidine on the prevention of catheter-related bloodstream infections in patients on home parenteral nutrition. J Vasc Access 2013;14(4):379—82.
[29] Geron R, Tanchilevski O, Kristal B. [Catheter lock solution-taurolock for prevention of catheter-related bacteremia in hemodialysis patients]. Harefuah;145(12):881-884, 943.
[30] Gudiol C, Nicolae S, Royo-Cebrecos C, Aguilar-Guisado M, Montero I, Martín-Gandul C, et al. Administration of taurolidine-citrate lock solution for prevention of central venous catheter infection in adult neutropenic haematological patients: a randomised, double-blinded, placebo-controlled trial (TAURCAT). Trials 2018;19(1).
[31] Handrup MM, Fuursted K, Funch P, Møller JK, Schrøder H. Biofilm formation in long-term central venous catheters in children with cancer: A randomized controlled open-labelled trial of taurolidine versus heparin. APMIS 2012;120(10):794—801.
[32] Jurewitsch B, Jeejeebhoy KN. Taurolidine lock: the key to prevention of recurrent catheter-related bloodstream infections. Clin Nutr 2005;24(3):462—5.
[33] Quarello F, Forneris G, Borca M, Pozzato M. Do central venous catheters have advantages over arteriovenous fistulas or grafts? J Nephrol 2006;19(3):265—79.
[34] Sodemann K, Polaschegg HD, Feldmer B. Two years' experience with Dialock and CLS (a new antimicrobial lock solution). Blood Purif 2001;19(2):251—4.
[35] Trivić I, Mišak Z, Kerman V, Prlić H, Kolaček S, Hojsak I. Central catheter-related bloodstream infection rates in children on home parenteral nutrition. J Pediatr Gastroenterol Nutr 2020;70(3):E59—62.
[36] Taniguchi A, Eastwood J, Davidson A, Nightingale J. Effectiveness of Taurolock™ in preventing recurrent catheter-related bloodstream infections in patients on home parenteral nutrition. Proc Nutr Soc 2009;68(OCE1):E58.
[37] Allon M. Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. Clin Infect Dis 2003;36(12):1539—44.
[38] Arnoriaga Rodríguez M, Pérez de Ciriza Cordeu M, Camblor Álvarez M, Bretón Lesmes I, Motilla de la Cámara M, Velasco Gimeno C, et al. Clinical and economic impact of the taurolidine lock on home parenteral nutrition. Nutr Hosp 2018;35(4):761—6.
[39] Bueloni TNV, Marchi D, Caetano C, de Souza Cavalcante R, Mendes Amaral ML, Ponce D. Cefazolin—gentamicin versus taurolidine—citrate for the prevention of infection in tunneled central catheters in hemodialysis patients: a quasi-experimental trial. International J Infect Dis 2019;85:16—21.
[40] Chong CY, Ong RY, Seah VX, Tan NW, Chan MY, Soh SY, et al. Taurolidine-citrate lock solution for the prevention of central line-associated bloodstream infection in paediatric haematology-oncology and gastrointestinal failure patients with high baseline central-line associated bloodstream infection rates. J Paediatr Child Health 2020;56(1):123—9.
[41] Chu HP, Brind J, Tomar R, Hill S. Significant reduction in central venous catheter-related bloodstream infections in children on HPN after starting treatment with taurolidine line lock. J Pediatr Gastroenterol Nutr 2012;55(4):403—7.
[42] Clark JE, Graham N, Kleidon T, Ullman A. Taurolidine-Citrate Line Locks Prevent Recurrent Central Line-Associated Bloodstream Infection in Pediatric Patients. Pediatr Infect Dis J 2019;38(1):e16—8.
[43] Cullis PS, McKee RF. Taurolidine lock - experience from the West of Scotland. Clin Nutr 2011;30(3):399—400.
[44] Fontseré N, Cardozo C, Donate J, Soriano A, Muros M, Pons M, et al. Tunneled catheters with taurolidine-citrate-heparin lock solution significantly improve the inflammatory profile of hemodialysis patients. Antimicrob Agents Chemother 2014;58(7):4180—4.
[45] Hulshof EC, Hanff LM, Olieman J, De Vette S, Driessen GJ, Meeussen C, et al. Taurolidine in pediatric home parenteral nutrition patients. Pediatr Infect Dis J 2017;36(2):233—5.
[46] Ince E, Oğuzkurt P, Temiz A, Ezer SS, Gezer HÖ, Yazici N, et al. Complications of total implantable access ports and efficacy of Taurolidine-citrate lock solution against catheter-related infections. Afr J Paediatr Surg 2014;11(2):138—42.
[47] Lambe C, Poisson C, Talbotec C, Goulet O. Strategies to reduce catheter-related bloodstream infections in pediatric patients receiving home parenteral nutrition: the efficacy of taurolidine-citrate prophylactic-locking. JPEN J Parenter Enteral Nutr 2018;42(6):1017—25.
[48] Murray EC, Deighan C, Geddes C, Thomson PC. Taurolidine-citrate-heparin catheter lock solution reduces staphylococcal bacteraemia rates in haemodialysis patients. QJM 2014;107(12):995—1000.
[49] Olthof ED, Versleijen MW, Huisman-de Waal G, Feuth T, Kievit W, Wanten GJ. Taurolidine lock is superior to heparin lock in the prevention of catheter related bloodstream infections and occlusions. PLoS One 2014;9(11):e111216.
[50] Saunders J, Naghibi M, Leach Z, Parsons C, King A, Smith T, et al. Taurolidine locks significantly reduce the incidence of catheter-related blood stream infections in high-risk patients on home parenteral nutrition. Eur J Clin Nutr 2015;69(2):282—4.
[51] Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM. Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. BMC Infect Dis 2008;8:102.
[52] Solomon LR, Cheesbrough JS, Bhargava R, Mitsides N, Heap M, Green G, et al. Observational study of need for thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin, taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. Semin Dial 2012;25(2):233—8.
[53] Toure A, Lauverjat M, Peraldi C, Boncompain-Gerard M, Gelas P, Barnoud D, et al. Taurolidine lock solution in the secondary prevention of central venous catheter-associated bloodstream infection in home parenteral nutrition patients. Clin Nutr 2012;31(4):567—70.
[54] Wouters Y, Roosenboom B, Causevic E, Kievit W, Groenewoud H, Wanten GJA. Clinical outcomes of home parenteral nutrition patients using taurolidine as catheter lock: A long-term cohort study. Clin Nutr 2019;38(5):2210—8.
[55] Ghais Fernández R, Saez Calero M, Yepez León F, Marín Franco A, Izquierdo Ortiz M, Santos Barajas J, et al. Profilaxis antimicrobiana en el sellado del catéter como medida adicional para la prevención de la bacteriemias asociadas a catéteres en pacientes en hemodiálisis. Diálisis y Trasplante 2018;39(2):32—42.
[56] Taylor C, Cahill J, Gerrish M, Little J. A new haemodialysis catheter-locking agent reduces infections in haemodialysis patients. J Ren Care 2008;34(3):116—20.
[57] Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. Nephrol Dial Transplant 2004;19(6):1546—51.
[58] Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ. Taurolidine lock is highly effective in preventing

catheter-related bloodstream infections in patients on home parenteral nutrition: a heparin-controlled prospective trial. Clin Nutr 2010;29(4):464—8.
[59] Dümichen MJ, Seeger K, Lode HN, Kühl JS, Ebell W, Degenhardt P, et al. Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. J Hosp Infect 2012;80(4):304—9.
[60] Filiopoulos V, Hadjiyannakos D, Koutis I, Trompouki S, Micha T, Lazarou D, et al. Approaches to prolong the use of uncuffed hemodialysis catheters: results of a randomized trial. Am J Nephrol 2011;33(3):260—8.
[61] Gudiol C, Arnan M, Aguilar-Guisado M, Royo-Cebrecos C, Sánchez-Orteg I, Montero I, et al. A randomized, double-blind, placebo-controlled trial (TAURCAT Study) of citrate lock solution for prevention of endoluminal central venous catheter infection in neutropenic hematological patients. Antimicrob Agents Chemother 2020;64:e01521. 19.
[62] Handrup MM, Møller JK, Schrøder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. Pediatr Blood Cancer 2013;60(8):1292—8.
[63] Klek S, Szczepanek K, Hermanowicz A, Galas A. Taurolidine lock in home parenteral nutrition in adults: results from an open-label randomized controlled clinical trial. JPEN J Parenter Enteral Nutr 2015;39(3):331—5.
[64] Longo R, Llorens M, Goetz C, Platini C, Eid N, Sellies J, et al. Taurolidine/citrate lock therapy for primary prevention of catheter-related infections in cancer patients: results of a prospective, randomized, phase IV trial (ATAPAC). Oncology 2017;93(2):99—105.
[65] Łyszkowska M, Kowalewski G, Szymczak M, Polnik D, Mikołajczyk A, Kaliciński P. Effects of prophylactic use of taurolidine-citrate lock on the number of catheter-related infections in children under 2 years of age undergoing surgery. J Hosp Infect 2019;103(2):223—6.
[66] Solomon LR, Cheesbrough JS, Ebah L, Al-Sayed T, Heap M, Millb, et al. A randomized double-blind controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. Am J Kidney Dis 2010;55(6):1060—8.
[67] Tribler S, Brandt CF, Petersen AH, Petersen JH, Fuglsang KA, Staun M, et al. Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal failure patients dependent on home parenteral support: a randomized, placebo-controlled trial. Am J Clin Nutr 2017;106(3):839—48.
[68] Winnicki W, Herkner H, Lorenz M, Handisurya A, Ž Kikić, Bielesz B, et al. Taurolidine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled hemodialysis catheters. Kidney Int 2018;93(3):753—60.
[69] Wouters Y, Theilla M, Singer P, Tribler S, Jeppesen PB, Pironi L, et al. Randomised clinical trial: 2% taurolidine versus 0.9% saline locking in patients on home parenteral nutrition. Aliment Pharmacol Ther 2018;48(4):410—22.
[70] Zwiech R, Adelt M, Chrul S. A taurolidine-citrate-heparin lock solution effectively eradicates pathogens from the catheter biofilm in hemodialysis patients. Am J Ther 2016;23(2):e363—8.
[71] Daoud DC, Wanten G, Joly F. Antimicrobial locks in patients receiving home parenteral nutrition. Nutrients 2020;12:439.
[72] Labriola L, Pochet JM. Any use for alternative lock solutions in the prevention of catheter-related blood stream infections? J Vasc Access 2017;18(Suppl. 1):34—8.
[73] Mandolfo S, Borlandelli S, Elli A. Catheter lock solutions: it's time for a change. J Vasc Access 2006;7(3):99—102.
[74] Norris LB, Kablaoui F, Brilhart MK, Bookstaver PB. Systematic review of antimicrobial lock therapy for prevention of central-line-associated bloodstream infections in adult and pediatric cancer patients. Int J Antimicrob Agents 2017;50(3):308—17.
[75] Vassallo M, Dunais B, Roger PM. Antimicrobial lock therapy in central-line associated bloodstream infections: a systematic review. Infection 2015;43(4):389—98.
[76] Prevention CDC. Device associated module BSI. 2021. Available at: http://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf [last accessed April 2021].