Review Article

Lock therapy in prevention and treatment of catheter-associated bloodstream infection: integrative review

Lock terapia na prevenção e tratamento da infecção da corrente sanguínea associada ao cateter vascular: revisão integrativa

Terapia de bloqueo en la prevención y tratamiento de infecciones del torrente sanguíneo asociadas al catéter vascular: revisión integradora

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Cateteres venosos centrais; Cateteres de demora; Dispositivos de acesso vascular; Infecções relacionadas ao cateter; Cuidados de enfermagem; Antibacterianos; Anti-Infecciosos; Lock terapia; Etanol

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Catéteres venosos centrales; Catéteres de permanencia; Dispositivos de acceso vascular; Infecciones relacionadas con catéteres; Cuidados de enfermería; Antibacterianos; Anti-Infecciosos; Lock terapía; Etanol

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Abstract

Objective: To synthesize knowledge on the use of lock therapy for prevention and treatment of long-term central vascular access devices-associated bloodstream infection in hospitalized adult and elderly patients.

Methods: Integrative review conducted in CINAHL, Cochrane Central, Embase, LILACS, PubMed, Scopus, and Web of Science databases, from January 1st, 2010 to September 28th, 2021, without language restrictions. Data were analyzed descriptively.

Results: Sixteen studies were identified, six (37.5%) on the use of lock therapy for prevention of bloodstream infection associated with central vascular access devices, and ten (62.5%) on treatment. The articles on prevention reported the use of non-antibiotic solutions. Nine of the ten studies that addressed lock therapy as treatment used antibiotic solutions. Two studies assessed the effectiveness of lock therapy in a short duration (three to four days), seven in a longer duration (between 10 and 14 days), and one did not specify the length of time. Each study described an intervention technique and the length of stay of the intraluminal solution. Regarding the risk of bias, five randomized clinical trials, two non-randomized clinical trials, and eight observational studies were rated as low risk. Only one observational study was classified as moderate risk.

Conclusion: The use of non-antibiotic solutions such as ethanol was identified for prevention of bloodstream infection. For treatment, intravenous daptomycin was used. While the studies included in this review on prevention did not show statistical evidence, the ten studies on treatment demonstrated that lock therapy is an effective complement to systemic treatment, showing good catheter salvage rates.

Resumo

Objetivo: Sintetizar o conhecimento sobre o uso da *lock* terapia na prevenção e no tratamento da infecção da corrente sanguínea associada ao dispositivo de acesso vascular central de longa permanência em pacientes adultos e idosos hospitalizados.

Métodos: Revisão integrativa com busca nas bases de dados *CINAHL*, *Cochrane Central*, *Embase*, *LILACS*, *PubMed*, *Scopus* e *Web of Science*, no período de 1º janeiro de 2010 a 28 de setembro de 2021 sem restrições de idioma. Os dados foram analisados de forma descritiva.

Resultados: Foram identificados 16 estudos sendo seis (37,5%) sobre o uso da *lock* terapia como prevenção de infecção associada ao dispositivo de acesso vascular central e dez (62,5%) sobre tratamento. Os artigos sobre prevenção relataram o uso de soluções não antibióticas. Nove dos dez estudos que abordaram a *lock* terapia como tratamento, utilizaram soluções antibióticas. Dois estudos avaliaram a eficácia da *lock* terapia em curta duração (de três a quatro dias), sete em maior duração (entre 10 e 14 dias) e um não especificou a duração. Cada estudo descreveu uma técnica de intervenção e o tempo de permanência da solução

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intraluminal. Em relação ao risco de viés, foram avaliados como baixo risco: cinco ensaios clínicos randomizados, dois ensaios clínicos sem randomização e oito estudos observacionais. Apenas um estudo observacional foi classificado como risco moderado.

Conclusão: Na prevenção, identificou-se o uso de soluções não antibióticas como o etanol. Para o tratamento, foi utilizada a daptomicina endovenosa. Enquanto os estudos incluídos nessa revisão sobre prevenção não demonstraram evidência estatística, os dez estudos sobre tratamento demonstraram que a *lock* terapia é um complemento eficaz ao tratamento sistêmico, apresentando boas taxas de salvamento do cateter.

Resumen

Objetivo: Sintetizar el conocimiento sobre el uso de la terapia de bloqueo en la prevención y tratamiento de infecciones del torrente sanguíneo asociadas al dispositivo de acceso vascular central de larga permanencia en pacientes adultos y adultos mayores hospitalizados.

Métodos: Revisión integradora con búsqueda en las bases de datos *CINAHL*, *Cochrane Central*, *Embase*, *LILACS*, *PubMed*, *Scopus* y *Web of Science*, en el período del 1 de enero de 2010 al 28 de septiembre de 2021 sin restricción de idioma. Los datos fueron analizados de forma descriptiva.

Resultados: Se identificaron 16 estudios, de los cuales seis (37,5 %) trataban sobre el uso de la terapia de bloqueo como prevención de infecciones asociadas al dispositivo de acceso vascular central y diez (62,5 %) sobre tratamiento. En los artículos sobre prevención se relató el uso de soluciones no antibióticas. En nueve de los diez estudios que abordaban la terapia de bloqueo como tratamiento, se utilizaron soluciones antibióticas. En dos estudios se evaluó la eficacia de la terapia de bloqueo de corta duración (de tres a cuatro días), siete de mayor duración (entre 10 y 14 días) y uno sin especificar la duración. En cada estudio se describió una técnica de intervención y el tiempo de permanencia de la solución intraluminal. Con relación al riesgo de sesgo, fueron evaluados con riesgo bajo: cinco ensayos clínicos aleatorizados, dos ensayos clínicos no aleatorizados y ocho estudios observacionales. Solo un estudio observacional fue clasificado con riesgo moderado.

Conclusión: Para la prevención, se identificó el uso de soluciones no antibióticas como el etanol. Para el tratamiento, se utilizó la daptomicina intravenosa. Aunque los estudios incluidos en esta revisión sobre prevención no hayan demostrado evidencia estadística, los diez estudios sobre tratamiento demostraron que la terapia de bloqueo es un complemento eficaz para el tratamiento sistémico y presentó buenos índices de salvamento del catéter.

Introduction

Intravascular devices are essential in the clinical management of hospitalized patients, particularly critically or chronically ill patients. The primary indications for the insertion of central vascular access devices (CVAD) are clinical instability of the patient and/or multiple infusions; inadequate continuous infusion therapy for peripheral lines (vesicant solutions, parenteral nutrition, electrolytes); invasive hemodynamic monitoring; long-term intermittent infusion therapy; and inability to provide other forms of venipuncture.[1,2]

When indicating a CVAD for any type of infusion therapy, the benefit must overcome the risk of complications.[1,3] Therefore, the risks associated with the use of catheters in hospitalized patients should be well known, including venous thrombosis and the increased risk of catheter- associated bloodstream infection (CABSI), which usually lead to a prolonged hospital stay, increased cost, and the risk of mortality.[1,4]

There are two main recognized routes of CABSI: migration of microorganisms from the skin around the insertion site to the cutaneous tract and catheter surface, which occurs during catheter's insertion and length of stay; and, direct contamination of the catheter hub by inappropriate handling during administration of intravenous therapy. The incidence of CABSI depends on catheter type and material, number of lumens, frequency of device manipulation, insertion site, length of stay, insertion technique, maintenance care, and patient-related factors such as underlying disease and severity.[1,3]

Therefore, lock therapy consists of the introduction of a locking solution into catheters that contains supratherapeutic concentrations of antimicrobials, and that can be combined with anticoagulants, for the treatment (therapeutic use) or prevention (prophylactic use) of CABSI. The solution is used to fill the lumen of the catheter, remaining for a period of time while the catheter is inactive. The permanence of the solution inside the catheter lumen can prevent the formation of biofilms and eliminate those that exist, preventing the appearance of CABSI.[1,4-6]

According to the Infusion Nurses Society's (INS) 2021 standards of practice for infusion therapy, the use of lock therapy in long-term CVADs is recommended in the following circumstances: high-risk patient populations, those with a history of multiple CABSI, and in institutions with unacceptably high rates of bloodstream infections associated with CVAD use, regardless of the implementation of other infection prevention methods.[1]

Long-term CVAD are those that remain in situ for more than 30 days.[1] The development of

standardized institutional lock solution protocols regarding formulation and preparation, indications of care, and situations for using this therapy can spread utilization and success of the therapy.[6]

Considering that lock therapy technique is still incipient, as there is insufficient evidence to indicate the optimal lock solution, dose, and duration for long-term CVAD. This review aimed to synthesize the knowledge on the use of lock therapy for prevention and treatment of long-term CVADs-associated bloodstream infection in hospitalized adult and elderly patients.

Methods

This is an integrative literature review conducted in six steps: identification of the theme, sampling, categorization of studies, evaluation of included studies, interpretation of results, and knowledge synthesis.[7]

The research question was formulated according to the PICOS strategy, Population (P) = adult and elderly hospitalized patient with long term CVAD, Intervention (I) = lock therapy, Comparison/control (C) = not applicable, Outcome (O) = prevention and treatment of long-term CVADs-associated bloodstream infection, and Study design (S) = original quantitative studies, published from 01/01/2010 to 28/09/2021, resulting in "How to perform lock therapy on long-term central vascular access devices of adult hospitalized patients, for prevention and treatment of long-term CVADs-associated bloodstream infection?"

Inclusion criteria included original studies involving hospitalized patients, aged 18 years or older, which evaluated the lock therapy technique in long-term CVAD, regarding the prevention and/or treatment of CABSI, considering different antimicrobial agents (antibiotics/antifungal or antiseptics), dosage, method of application, and time the substance remains in the lumen of the intravascular catheter.

Exclusion criteria were studies performed with hemodialysis catheters or catheters used exclusively for total parenteral nutrition (TPN), studies that evaluated lock therapy in vitro or in animals, and those derived from gray literature.

The search was performed on September 28th, 2021, in the CINAHL, Central Cochrane Library, Embase, LILACS, PubMed, Scopus, and Web of Science databases. No language restrictions were imposed.

The search strategy was based on the research question, and adapted for each database. Controlled descriptors were used in the singular and plural forms, according to the example of the search conducted in PubMed, described as: ((("central venous catheters"[MeSH] OR "central venous catheters" OR "central venous catheter" OR "catheterization, central venous"[MeSH] OR "catheterization, central venous" OR "central venous catheterization" OR "central venous catheterizations" OR "central venous access" OR "implantable vascular access" OR "catheters, indwelling"[MeSH] OR "catheters, indwelling" OR "indwelling catheter" OR "indwelling catheters" OR "in-dwelling catheters" OR "in-dwelling catheter" OR "hickman catheter" OR "hickman catheters" OR "broviac catheter" OR "broviac catheters" OR "cook catheter" OR "vascular access devices"[MeSH:NoExp] OR "vascular access devices" OR "vascular access device" OR "vascular catheters" OR "vascular catheter" OR "long-term catheters" OR "long-term catheter" OR "tunneled central venous catheters" OR "tunneled central venous catheter" OR "renal dialysis" [MeSH:noexp] OR "catheterization, peripheral"[MeSH] OR "catheterization, peripheral" OR "peripheral catheterization" OR "peripheral catheterizations" OR "peripherally inserted central catheter line insertion" OR "peripheral venous catheterization" OR "peripheral venous catheterizations")) AND Lock*) AND ("catheter-related infections"[MeSH] OR "catheter related infections" OR "catheter related infection" OR "catheter-related bloodstream infection" OR "intravascular catheter-related bloodstream infection").

The references identified were exported to the online EndNote manager, and after removing the duplicates, the remaining studies were transferred to the Rayyan web application for reading of titles and abstracts.[8,9]

All relevant full articles were retrieved and reviewed independently by two reviewers, according to the proposed eligibility criteria. A third reviewer was responsible for resolving conflicts.

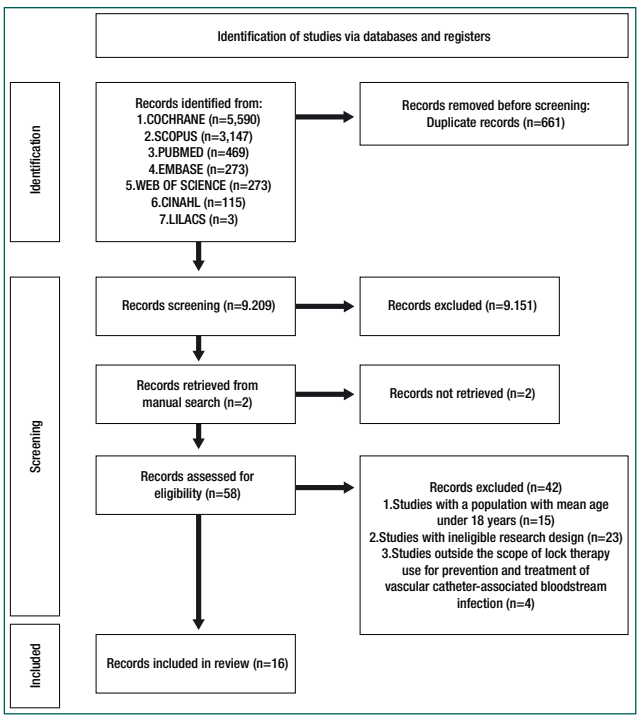
Relevant information from each article selected for the final sample was independently extracted by the two reviewers, and disagreements were resolved with a third reviewer. The data extraction included study characteristics, population, intervention, and main outcomes.

Three tools were adopted to assess the risk of bias, according to each type of study. For randomized clinical trials the Risk-of-Bias Tool for Randomized Trials (RoB 2), proposed by the Cochrane Collaboration, was used.[10] For non-randomized clinical trials, the tool proposed by the Joanna Briggs Institute (JBI) was implemented.[11] For observational studies, the AXIS tool was used.[12] The analyses were performed by two independent reviewers.

The classification of non-randomized clinical trials and observational studies followed the methodological quality categorization proposed by Polmann et al. (2019),[13] which considers as high risk of bias when the study achieved a "yes" score above 49%, moderate between 50% and 69%, and low for above 70%.

Results

After searching the electronic databases, 9,870 documents were identified, of which 661 were duplicates and were removed. After reading the titles and abstracts of 9,209 documents, 58 articles were selected to be full-text reading. After reading the full-text, the studies were selected according to predefined eligibility criteria, resulting in the exclusion of 42 articles. Sixteen studies were selected for this integrative review. A detailed flowchart of the selection process is shown in Figure 1. In Charts 1 and 2, there is a summary of the studies included in this review, classified in prevention and treatment of CABSI.[15-30] Three studies were from the United States of America (USA). The Netherlands, France, India and Spain contributed to two studies each. Denmark, Italy, Germany, Australia and Brazil contributed to one study each. All studies that comprise this review were published in medical journals, of which four studies (26.7%) were from the American journal called Antimicrobial Agents and Chemotherapy. The predominant method used to assess the efficacy of lock therapy in the prevention and treatment of CABSI was observational, representing 56.3% (n=9) of the total.[15-22,30] Intervention studies were responsible for 43.7% (n=7) of the studies, of which five were randomized clinical trials [23-27] and two were non-randomized clinical trials.[28,29]



Source: Adapted from PAGE et al., 2021.[14]

Figure 1. Integrative review flowchart adapted from PRISMA

Regarding the risk of bias of the nine observational studies included in this review, eight were classified as low risk and one as moderate risk of bias (Figure 2).

The two non-randomized clinical trials [28,29] were rated as having low risk of bias. The studies met the categories of clarity about the "cause" and "effect" of the variables, inclusion of participants according to some similar comparison, measurements

Table 1. Synthesis of studies included in the integrative review addressing lock therapy in the prevention of catheter-associated bloodstream infection

Author, year, country	Study design	Objective	Intervention	Control	Main results
Slobbe et al., 2010.[23] Netherlands	Placebo-controlled randomized clinical trial	To study the efficacy and safety of daily lock therapy with 70% ethanol in the prevention of endoluminal CABSI in hematologic patients with long-stay tunneled catheters.	The lumens of CVAD were locked for 15 min/day with 3 ml of 70% Ethanol daily during hospitalization. Afterwards the lumens were flushed with 10 ml of 0.9% NaCl .	Lock therapy with placebo.	For lock therapy with ethanol, the incidence of endoluminal CABSI per 1000 catheters/day was 0.70 compared to 1.19 in the placebo group, with a non-significant 41% reduction in patients receiving lock therapy with ethanol (p=0.19 For endoluminal CABSI, a non-significant 3.6-fold reduction was found for patients receiving ethanol (2 of 226 versus 7 of 222; p=0.103). More patients receiving ethanol lock therapy discontinued treatment (11 of 226 versus 1 of 222; p=0.006) or continued, with less frequent lock therapy administration (10 of 226 versus 0 of 222; p=0.002), due to non-severe adverse events. Total N=376 patients with 448 catheter
Boersma et al., 2014.[24] Netherlands	Randomized clinical trial	To determine the efficacy of lock therapy with TSC compared to heparin in preventing thrombosis and infections associated with tunneled or non-tunneled CVAD in patients with hematologic malignancies undergoing high-dose chemotherapy.	After each catheter use, the lumen was flushed with 10 ml of 0.9% NaCl and locked with 46.7% citrate.	After CVAD use, each lumen received lock therapy with heparin sodium 5,000 U/ ml.	34 episodes of CABSI occurred in the 108 patients who were treated with heparin lock therapy compared to 35 episodes in the 99 patients who received lock therapy with TSC (p=0.654). Seven times more CABSI were found with gram-negative batonettes in the heparin lock therapy (p=0.041). Total N=207 patients.
Worth et al., 2014.[25] Australia	Randomized clinical trial	To prospectively compare heparinized saline solution with ethanol 70% as lock therapy in hematologic or hematopoietic stem cell transplant patients with tunneled CVAD (prevention).	Each lumen was flushed with 10 ml of saline solution and locked with 2 ml of 70% ethanol, with a dwell time of 2 hours.	Daily lock therapy with heparinized saline solution with a dwell time of 2h in the catheter lumen.	Central catheter-associated bloodstream infection rates were 6.0 in the control group and 4.1 in the intervention group per 1,000 CVAD days (p=0.42). Five CABSI events were identified over 1,917 days of CVAD in the heparinized saline group. Four CABSI events were detected over 1,381 days of CVAD in the ethanol group (p=1.00). Outlet site infection was detected in three patients receiving heparinized saline and in two patients receiving ethanol. N total=85 patients
Gudiol et al., 2020.[26] Spain	Multicenter double-blind randomized clinical trial	To test the efficacy of lock therapy with taurolidine-citrate-heparin solution compared to placebo, for prevention of CVAD infection in hematologic neutropenic patients.	Each lumen was locked with 2.5ml of taurolidine 2%, citrate 4% and heparin 500UI/ml solution, three times a week, every 48/72h and dwell time of two hours.	Same procedure with placebo solution. .	Lock therapy with taurolidine-citrate-heparin was associated with less CVAD hub colonization compared to placebo solution: three patients in the intervention group (4.1%) versus seven patients in the placebo group (10.1%). There were no significant differences regarding the incidence of CABSI: two episodes in the intervention group and one in the placebo group. CVAD was removed in 13 patients in each group. N total=141 patients.
Longo et al., 2017.[27] France	Randomized, prospective, single-center, phase IV clinical trial	To evaluate the efficacy of lock therapy with taurolidine versus saline solution for prevention of primary infection associated with the fully implanted catheter of oncologic, non-hematologic patients receiving intravenous chemotherapy.	Lock therapy with 3 ml of taurolidine solution	Lock therapy with saline solution.	The incidence rate of CABSI in totally implanted catheter was 0.4% catheters/day in the control group and 0.1% catheters/day in the taurolidine group (p=0.21). Totally implanted catheter-associated infections required 22 days of hospitalization in the taurolidine group versus 106 days in the control group. Taurolidine-related toxicity was transient and classified as grade I. Total number=163 patients
Chaftari et al., 2017.[29] USA	Pilot, open-label, prospective study	To evaluate the efficacy and safety of a nonantibiotic and nonheparin nitroglycerin-based lock solution, for the prevention of CABSI in cancer patients using peripherally inserted central catheter.	Lumens were flushed with 0.9% NaCl, followed by infusion of a 2 hour once daily combination of 0.8 to 1 ml of solution composed of 15 or 30 µ Nitroglycerin, 4% sodium citrate and 22% ethanol	Each patient served as his own control while he was not receiving the study solution, but was receiving heparin or saline.	No CABSI was identified during the 619 catheters/day with administration of the lock therapy solution, compared to three episodes of CABSI during the 1,853 days without lock therapy (p=0.32). There were no serious adverse events or episodes of hypotension related to the lock therapy administration. The rate of CABSI was zero on lock therapy days versus 1.6/1,000 catheters/day without lock therapy, compared to a rate of 1.9/1,000 catheters/day in the same patient population. Total N=60 patients.

CABSI:catheter-associated bloodstream infection, CVAD: central vascular access devices, NaCl: sodium chloride, TSC: Trisodium citrate

Table 2. Summary of studies included in the integrative review addressing lock therapy in the treatment of catheter-associated bloodstream infection

Author, year, country	Study design	Objective	Intervention	Control	Main results
Ahmad et al., 2019.[15] denmark	Retrospective, non-interventional quality control study	To analyze the dwell time of the tunneled catheter after hydrochloric acid installation in adult hematologic patients with CABSI (treatment).	Each lumen was flushed with 10 ml of 0.9% NaCl; administered hydrochloric acid 2.5 mmol/ml according to lumen volume; 10 minutes of dwell time; 5 ml aspirated from each lumen; flushed with 10 ml of 0.9% NaCl; the procedure was repeated two more times.	Not applicable.	After lock therapy with hydrochloric acid, the CVAD was not removed due to infection in 49 of 71 patients (69%). 22 patients (31%) kept their CVAD until the end of treatment. Non-infectious mortality (19/71), accidental removal (2/71) or mechanical dysfunction of the CVAD (6/71) were additional reasons for premature catheter removal. Twenty-two catheters (31%) had to be removed because of infection. The median time from CVAD insertion to hydrochloric acid lock therapy was 39 days. The median time from hydrochloric acid lock therapy to CVAD removal was 58 days. N total=75 patients
Bookstaver et al., 2010.[16] USA	Retrospective analysis of a case series	To analyze the outcomes associated with antimicrobial lock therapy as adjuvant treatment of CABSI.	Lumens were maintained with lock solution whenever the CVAD was not in use, and subsequently, suctioned. In double lumen CVAD, one was maintained with locking solution for 24h, alternating every other day.	Not applicable.	Most patients received vancomycin, daptomycin or gentamicin combined with heparin as lock therapy. Negative blood culture was achieved in 69.2% of cases and negative blood culture plus CVAD maintenance was achieved in 11 cases (42.3%). Longer length of antimicrobial lock therapy was significantly correlated with negative blood culture (p=0.077). Total N=26 cases in 15 patients.
Freire et al., 2018.[17] Brazil	Prospective study	To analyze long-term CVAD associated infections from risk factors for unfavorable outcomes and the impact of lock antimicrobial therapy, including multidrug-resistant bacteria infection (treatment).	Vancomycin (5mg/ml) and Amikacin (2mg/ml) administered in all lumens, changed every 24h.	Systemic treatment, no lock therapy.	296 infections associated with long-term CVAD were identified, 212 (71.6%) were bloodstream infections. The success rate of antimicrobial lock therapy was 75.9%. Despite high incidence of infection by multidrug-resistant bacteria, antimicrobial lock therapy improved the outcome of long-term CVAD-associated infection in cancer patients.Total number: 275 patients with 296 infections
Haag et al., 2011.[18] Germany	Retrospective analysis of a case series	To evaluate lock therapy with taurolidine in combination with systemic antibiotic in the management of CABSI.	CVAD was locked for 3 to 4 consecutive days with TauroLock™ Hep 100R solution (cyclotaurolidine 1.4%, citrate solution 0.4% and heparin 100UI/ml).	Not applicable.	Treatment was successful in 16 of 24 events (67%). CVAD removal was required in 8 cases (33%). In four patients, the conservative approach was discontinued prematurely due to persistent fever. N total=23 patients with 24 episodes of infections
Soman et al., 2016.[19] Índia	Exploratory study	To explore the use of new antimicrobials for lock therapy in long term catheter (treatment).	Antibiotic solution associated with N-acetylcystin 20%- 2ml and heparin 50-100UI in a volume sufficient to fill the catheter lumen, remaining for 24h, 14 consecutive days.	Not applicable.	Treatment with lock therapy was successful in 30 (81.08%) of 37 episodes of CABSI/symptomatic colonization. The catheter was saved in 26 (86.66%) of the 30 episodes caused by GNB and in 2 of 4 episodes caused by GPC. Lock therapy failure was evidenced in CABSI by *Stenotrophomonas*, *Pseudomonas*, *Acinetobacter baumanii*, methicillin-resistant *Staphylococcus aureus* and coagulase negative *Staphylococcus*. Two patients had the catheter removed due to obstruction, both had negative catheter tip cultures. In two episodes Colistin was successfully used in lock therapy. N total=29 patients with 37 episodes of infection.
Tatarelli et al., 2015.[20] Italy	Retrospective analysis of a case series	To analyze the efficacy of daptomycin administered systemically and as lock therapy in the treatment of CABSI.	5 ml of daptomycin solution diluted in Ringer's lactate at a dose of 1mg/ml administered into each lumen, remaining for 12h/day.	Not applicable.	Seven patients failed previous therapy with Vancomycin and one patient with cefazolin. Daptomycin was successful in six (75%) of the eight cases (clinical improvement and microbiological eradication). The mean duration of daptomycin therapy was 13 days (range 7-16). N total=8 patients
Vassallo et al., 2017.[21] France	Retrospective cohort study	To evaluate the efficacy of the antibiotic lock therapy combined with systemic daptomycin for conservative treatment of implanted catheters in patients with CoNS infection	5 ml of daptomycin, 25 mg solution diluted in lactated ringer's solution at a dose of 5mg/ml administered into each lumen, maintained for 18h daily for three consecutive days.	Not applicable	21 episodes of CABSI were analyzed among 20 patients. The mean duration of antibiotic lock therapy combined with systemic daptomycin was three days, with rifampicin for four days, followed by switching to oral medications, most commonly cotrimoxazole or linezolid to a mean of 14 days of treatment. Clinical success and failure rates were 76% and 24%, respectively. Total N=20 patients with 28 episodes of infection.
Zanwar et al., 2018.[22] Índia	Retrospective study	To analyze the incidence, microbiological and treatment patterns, and efficacy of antibiotic lock therapy for colonized tunneled catheters (Hickman) and CABSI in patients undergoing hematopoietic stem cell transplantation (treatment).	Catheter contents suctioned; catheter flushed with saline solution; antibiotic administered according to the microorganism sensitivity, in a volume appropriate to the lumen; dwell time of 24 hours; procedure repeated after 24 hours.	Not applicable.	Incidence of catheter colonization was 9.8%, and in 45% of the cases the microorganism was BGN. The incidence of CABSI was 10.7%, and in 83% of cases the microorganism was BGN. Hickman catheter salvage rate in patients with CABSI submitted to antibiotic lock therapy combined with systemic antibiotic therapy was 86% compared to 55% rate in patients without lock therapy (p=0.06). There was no increase in resistant strains subsequent to CABSI. N total=224

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Author, year, country	Study design	Objective	Intervention	Control	Main results
Raad et al., 2016.[28] USA	Phase II Pilot Study	To evaluate the efficacy of the triple combination of 1 mg/ml minocycline and 30 mg/ml EDTA in 25% ethanol (MLT) to rescue catheters with CABSI, allowing the treatment of these infections without removal of the CVAD.	Each catheter lumen was filled with 0.8 to 1 ml of the MLT solution for 2h, once a day, for a total of 7 doses. Five were in the first five subsequent days and the last two doses in the following two weeks.	Patients with CABSI who have had the catheter removed, with the insertion of a new CVAD.	The time for fever remission and microbiological eradication were similar in both groups. Patients in the intervention group received systemic antibiotic therapy for a shorter time than patients in the control group (median 11 days versus 16 days, respectively; p<0.0001). Patients who received lock therapy maintained the catheter for a median of 74 days (4-240 days) after the onset of bacteremia. No patients who received lock therapy had infectious or mechanical complications compared to the control group, where seven infectious and six mechanical complications were found. N total=90 patients
Alonso et al., 2020[30] Spain	Retrospective study	To evaluate the success of lock therapy with vancomycin solution combined with systemic antimicrobials for the treatment of patients with staphylococcal CABSI.	Each catheter lumen or reservoir was locked daily with 2 ml of solution containing vancomycin (5 mg/ml) and heparin (60 IU) for a period of 8-12 to 24 h for 7-14 days.	Not applicable.	42.1% of 72 patients on vancomycin solution lock therapy remained with CVAD after CRBS. When considering the dwell time until catheter replacement or end of therapy, the success rate was higher (71.1%). No significant differences regarding catheter type, age, length of hospital stay, minimum inhibitory concentration of vancomycin, and *Staphylococcus* species was found. Although the crude mortality rate was 53.9%, the mortality rate attributable to CRBS was 1.3%.

CABSI:catheter-associated bloodstream infection, CVAD: central vascular access devices, NaCl: sodium chloride, TSC: Trisodium citrate, EDTA: Ethylenediamine tetraacetic acid, MLT: Minocycline lock therapy GNB: Gram-negative bacilli, CoNS: Coagulase-negative staphylococci , GPC: Gram-positive cocci

STUDIES	Objectives of the study	Study design	Sample size	Reference population	Sampling frame	Participant selection	Non-responder	Adequacy of variables	Measurment of variables	Statistical significance	Reproducibility of the method	Data description	Non-response bias	Description non-respondents	Consistency of results	Presentation of results	Discussion and conclusion	Study limitations	Conflit of interest	Ethics in conducting the study	Score % (sim)
Alonso et al, 2020.[30]	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	85
Bookstaver et al., 2010.[16]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	?	?	75
Haag et al., 2011.[18]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	?	+	?	75
Tatarelli et al., 2015.[20]	+	+	+	+	+	?	-	+	+	+	?	?	?	-	+	+	+	+	+	?	65
Soman et al., 2016.[19]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	?	?	85
Vassallo et al., 2017.[21]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	+	?	80
Zanwar et al., 2018.[22]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	+	+	85
Freire et al., 2018.[17]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	+	+	85
Ahmad et al., 2019.[15]	+	+	+	+	+	+	-	+	+	+	+	+	?	-	+	+	+	+	+	+	85

(+) yes; (-) no; (?)not known

Figure 2. Methodological quality assessment using the AXIS tool for observational studies categorized by the authors, and considered high risk of bias when the study achieved a "yes" score below 49%, moderate between 50% and 69%, and low for above 70%.

of outcome before and after the intervention, complete follow-up, and if this was not possible, the description and analysis of differences between groups in terms of follow-up, form and reliability of outcome measurement, and statistical analysis. The five randomized clinical trials[23-27] were rated as having low risk of bias in the five categories assessed: randomization process, deviations from assigned interventions, lack of outcome data, outcome measurement, and selection of reported outcome.

Discussion

The use of long-term CVAD has increased in recent decades as a result of the requirements of critically ill, hematologic-oncologic patients, as well as patients on TPN and hemodialysis. Cases of CABSI have a considerable impact on this population, increasing mortality, length of hospital stay, and worsening the quality of the patient's life, which often implies that the only possible intra-

vascular access is lost, and consequently increases hospital costs.[31-33]

Cases of CABSI often require removal of the CVAD, however, it might not be possible in cases of extremely limited alternative vascular access or complications associated with catheter removal and insertion of a new device. In such instances, catheter salvage is desired. Therefore, antimicrobial lock therapy is recommended in addition to parenteral antimicrobial therapy to save the catheter, and must be used for 10 to 14 days.[22,34] Lock therapy is also indicated for prophylaxis of CABSI in patients with long-term catheters, history of multiple CABSI, especially oncology and dialysis patients. In this study, we did not evaluate the different lock therapy techniques, which differ among specific populations, such as in patients using CVADs for hemodialysis.[1]

Central Venous Access Device removal is indicated in patients with: suspected CABSI and hemodynamic instability; severe sepsis; endocarditis; septic thrombophlebitis; persistent bacteremia after more than 72 hours of adequate antimicrobial therapy; CABSI due to *Staphylococcus aureus*, multidrug-resistant gram-negative bacilli, Micrococcusspp, Propionibacterium, mycobacteria, or fungi. Infections that occur soon after catheter insertion (less than 2 weeks) are usually extraluminal, and the lock therapy may not have the expected effect in the treatment of CABSI.[22,34]

The properties of an ideal antibiotic lock therapy solution include intrinsic antimicrobial activity against the microorganism causing CABSI, ability to penetrate and disrupt biofilm cells, compatibility with the anticoagulant agent in use, prolonged stability, minimal risk of toxicity, low resistance potential, compatibility with catheter materials, and cost-effectiveness.[6]

The Infusion Nurses Society (INS) recommends initiating catheter treatment via lock therapy within 48 to 72 hours of diagnosis, with antibiotics for CABSI. The INS states that the dwell time of antimicrobial lock therapy solutions remaining within the lumen of the DAVC is unknown, and may require up to 12 hours per day, limiting its use in patients receiving intermittent infusions. However, the optimal time of use has not been established. [1]

Some studies and institutional protocols suggest using a volume of lock therapy solution sufficient to fill the catheter lumen, and that the minimum dwell time should be two to four hours. The concentration of the antibiotic in the lock therapy can decrease substantially over time, therefore, the antibiotic lock solution should be changed at least every 48 hours.[34]

Antibiotics such as vancomycin and gentamicin are usually used for therapeutic measures once the CABSI is diagnosed. In contrast, antiseptic solutions such as ethanol, citrate, ethylenediaminetetraacetic acid (EDTA) and, increasingly, taurolidine are employed for prophylaxis. More experience is emerging in the treatment and prevention of CABSI infections using lock therapy.[31]

Cost-benefit analysis of antimicrobial lock therapy compared to heparin lock therapy in the prevention of CABSI showed that antimicrobial solutions (antibiotic or antiseptic solutions) has about an 88% chance of being cost-effective among patients in the oncology sector. This finding indicates that lock therapy associated with effective prevention interventions already adopted by health care services, such as appropriate selection of the catheter insertion site, optimal catheter selection, aseptical catheter insertion technique, and proper catheter handling techniques, may decrease infection rates.[35] Furthermore, heparin use may stimulate *Staphylococcus aureus* biofilm development.[1]

Ethanol is an effective antiseptic against a wide range of microorganisms, including bacteria and fungi, without known acquired resistance. However, limited prospective randomized studies evaluating its efficacy and safety are available. Although ethanol lock solution has been shown to be effective in eliminating bacterial growth, no knowledge of the safety profile for its use is yet available, such as the effect of ethanol on plasma proteins and erythrocytes in whole blood or on catheter integrity. Ethanol may increase the risk of hemolysis, as well as precipitate plasma proteins in a dose-dependent manner, resulting in catheter obstruction. Concentrations higher than 40% ethanol are correlated with increased *Staphylococcus aureus* biofilm, and polyurethane catheters have

shown changes in their mechanical properties after exposure to ethanol. [36,37]

Ethanol can also, in situations of inadvertent flushing, be associated with some adverse effects, such as systemic symptoms of dizziness, mental confusion, and elevation of liver function tests. The Infectious Disease Society of America (IDSA) does not recommend lock therapy with ethanol 70%.[3,36,37]

These factors associated with ethanol recommend the use of taurolidine. Taurolidine is a derivative of the amino acid taurine, which has broad antimicrobial activity including against gram-positive and gram-negative organisms and fungi.[38] A systematic review on lock therapy for prevention of CABSI showed that taurolidine, in most of the studies analyzed, reduced infection rates. However, adverse events were identified after its administration, such as flushing, abnormal taste, nausea, vomiting, chest and neck discomfort, and perioral dysesthesia.[39] A meta-analysis on pediatric patients indicated that taurolidine can significantly reduce CABSI, although the studies analyzed had a low quality of evidence.[38]

Taurolidine is available in Brazil as Taurolock™ in three and five ml unit dose vials, and 100 ml multiple dose vials. For the use of both ethanol and taurolidine, the indication of doses or duration of intervention are varied, as observed in the primary studies included in this review.[18,23,25-27]

The use of sodium citrate, an anticoagulant with antimicrobial effects for systemic anticoagulation, should be monitored, as it may trigger hypocalcemia that could cause cardiac arrest, and protein precipitate formation at concentrations higher than 12%.[1]

The articles included in this review showed lock therapy to be potentially effective in the prevention of CABSI,[23-27,29] as well as in the their treatment, in combination with systemic antimicrobial therapy to save the CVAD. Further clinical trials with specific agents and duration of therapy are needed.[15-22,28]

Although lock therapy represents a valuable option, its use includes logistical challenges, such as lack of familiarity with the technique and standardized protocols for use. The adoption of lock therapy requires the development of evidence-based local recommendations, with standardization of antibiotic concentrations, use of additives such as anticoagulants, expiration time of solutions, definition of indications, duration of therapy, and dwell time of solutions.[6]

This discussion requires the presence of the nurse, which is the professional responsible for maintenance and care of the catheter. It is therefore necessary that nurses are updated on lock therapy technique, compatibility of catheter material and intravenous solutions with the lock solution, adjusting the use of lumens, their labeling, ensuring that solutions are removed at the end of the procedure, preventing their introduction into the bloodstream; and it is required that the nursing team is properly oriented to effectively use lock therapy without risks to the patient.

An interdisciplinary approach is required for effective lock therapy. There should be referral to a pharmacist to ensure that the combined solutions are physically compatible, chemically stable, and will produce the desired antimicrobial effect.[1]

The limitations of this study include the wide variety of compounds used, the different patient populations studied, and limitations in the size or design of the studies, which preclude a general recommendation for use.

No evidence was found in this review to recommend the administration of lock therapy with non-antibiotic antimicrobials for prevention of CABSI. To reduce the risk of bloodstream infection, the INS recommends that a commercially filled, single-dose, ready-to-use syringe with appropriate solution is used for flushing and locking CVADs to decrease the risk of contamination when diluting the lock solution.[1] With regard to the solution, we identified the use of taurolidine and ethanol, with taurolidine having fewer adverse events in its administration.

Regarding the treatment of CABSI, in agreement with the INS, we have found that lock therapy with antibiotics is an effective complement to systemic treatment, with good catheter salvage rates, especially using intravenous daptomycin. The

INS even recommends attempting catheter salvage in patients with uncomplicated CABSI on a long-term CVAD colonized by coagulase-negative *Staphylococcus* or *Enterococcus*, while maintaining strict clinical monitoring.[1]

The INS[1] guidance for lock therapy administration is to begin by disinfecting the connection surfaces, flush the CVAD routes with preservative-free 0.9% sodium chloride, using a volume at least equal to or twice the internal volume of the catheter system. The volume of flushing depends on the type and size of catheter, age of the patient, and type of infusion therapy administered. A larger volume can remove more fibrin deposits, medication precipitate, and other debris from the lumen, and is recommended when infusing blood products, blood samples, parenteral nutrition, contrast media, and other viscous solutions. When using bacteriostatic 0.9% sodium chloride, the flushing volume should be limited to no more than 30 ml over a 24 hour period to reduce the possible toxic effects of the preservative, benzyl alcohol. Dextrose should not remain in the catheter lumen, as it provides nutrients for biofilm growth. After the final flushing is complete, each lumen of the CVAD should be blocked to reduce the risk of intraluminal occlusion. If multi-dose bottles are required, one should be dedicated to a single patient, stored according to the manufacturer's guidelines, while maintaining sterility.

Conclusion

Six primary studies related to the prevention of CABSI with lock therapy were identified, where the use of antiseptic substances such as ethanol was identified. Taurolidine was reported to be used both for prevention and treatment in three primary studies. With regard to lock therapy treatment, ten studies were synthesized and six of them addressed the use of antibiotics selected from the antibiogram, with daptomycin identified in three studies. The use of taurolidine is recommended instead of ethanol, due to fewer adverse events. New solutions, such as nitroglycerin and trisodium citrate, need further studies to assess their efficacy. While the studies on prevention showed no statistical evidence, the nine treatment studies demonstrated that lock therapy is an effective complement to systemic treatment of CABSI, with good rates of rescue and salvage of CVAD.

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