JVA
ISSN 1129-7298

J Vasc Access 2016; 17 (6): 453-464
DOI: 10.5301/jva.5000576

REVIEW

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

Mauro Pittiruti[1], Sergio Bertoglio[2], Giancarlo Scoppettuolo[1], Roberto Biffi[3], Massimo Lamperti[4], Alberto Dal Molin[5], Nicola Panocchia[1], Nicola Petrosillo[6], Mario Venditti[7], Carla Rigo[8], Enrico DeLutio[9]

[1] Fondazione Policlinico Universitario "A. Gemelli", Rome - Italy
[2] Department of Surgical Sciences, Università degli Studi, Genova - Italy
[3] Istituto Europeo di Oncologia, Milan - Italy
[4] Cleveland Clinic Hospital, Abu Dhabi - United Arab Emirates
[5] Università del Piemonte Orientale, Biella - Italy
[6] Istituto Nazionale Malattie Infettive "L. Spallanzani", Rome - Italy
[7] Università "La Sapienza", Rome - Italy
[8] Azienda Ospedaliera Universitaria "Maggiore della Carità", Novara - Italy
[9] Vascular Access Specialist, Rome - Italy

ABSTRACT

Background: The most appropriate lock solution for central venous access devices is still to be defined. GAVeCeLT – the Italian group for venous access devices – has developed a consensus on the evidence-based criteria for the choice and the clinical use of the most appropriate lock solution for central venous catheters (excluding dialysis catheters).

Method: After the constitution of a panel of experts, a systematic collection and review of the literature has been performed, focusing on clinical studies dealing with lock solutions used for prevention of occlusion (heparin, citrate, urokinase, recombinant tissue plasminogen activator [r-TPA], normal saline) or for prevention of infection (citrate, ethanol, taurolidine, ethylene-diamine-tetra-acetic acid [EDTA], vancomycin, linezolid and other antibiotics), in both adults and in pediatric patients. Studies on central lines used for dialysis or pheresis, on peripheral venous lines and on arterial lines were excluded from this analysis. Studies on lock solutions used for treatment of obstruction or infection were not considered. The consensus has been carried out according to the Delphi method.

Results: The panel has concluded that: (a) there is no evidence supporting the heparin lock; (b) the prevention of occlusion is based on the proper flushing and locking technique with normal saline; (c) the most appropriate lock solution for infection prevention should include citrate and/or taurolidine, which have both anti-bacterial and anti-biofilm activity, with negligible undesired effects if compared to antibiotics; (d) the patient populations most likely to benefit from citrate/taurolidine lock are yet to be defined.

Conclusions: The actual value of heparinization for non-dialysis catheters should be reconsidered. Also, the use of lock with substances with anti-bacterial and anti-biofilm activity (such as citrate or taurolidine) should be taken into consideration in selected populations of patients.

Keywords: Central venous catheters, Citrate, Flushing, Heparin, Lock solution, Taurolidine

Accepted: May 8, 2016
Published online: August 1, 2016

Corresponding author:
Mauro Pittiruti, MD
Università Cattolica del Sacro Cuore
Fondazione Policlinico Universitario 'A. Gemelli'
Largo Francesco Vito 1
00168 Roma, Italy
mauro.pittiruti@policlinicogemelli.it

Introduction

There is a wide consensus that a central venous line – if used discontinuously – should be periodically flushed with normal saline, so to remove traces of the previously infused solutions; also, as the line is closed, it should be filled with a 'lock solution', which may have anticoagulant action, and/or an antibacterial action, or – as in the case of normal saline – no specific action at all.

Recommendations about flushing and locking the venous access device in the interval between infusions are included in all standard management policies, as a relevant issue in preventing complications. For a better understanding of the details of such procedures, a clear definition of the terms 'flush' and 'lock' is particularly important. As a matter of fact, the terms 'flush' and 'lock' are sometimes mutually exchanged and ambiguously defined in guidelines and literature, thus leading to confusion and misunderstanding. The 'flush' in an intravascular catheter is defined as the manual injection of a solution, generally normal saline, with the purpose of cleaning the inner lumen of the catheter, removing remnants of infused substances and maintaining its patency. The 'lock' is generally defined as the intraluminal injection of a limited volume of fluid, after the catheter flush, in the intervals of time when the catheter is not in use, with the purpose of preventing lumen occlusion and/or bacterial colonization (1). There are several methodologies of flushing and locking but none of them is universally accepted as a standard of practice.

While everyone agrees that the 'flush' of any venous access device is mandatory after its use and that such flush should be done with normal saline, the optimal 'lock' of the venous access is still largely controversial, depending on the type of venous access and on its use, the main differences being, for example, between peripheral venous access devices (PVAs) and central venous access devices (CVAs), or between central venous catheters intermittently used for blood exchange procedures, such as dialysis or apheresis (dialysis central venous access, [DCVA]) and central venous lines used not for dialysis or apheresis but for intravenous drug infusion, parenteral nutrition, chemotherapy, blood sampling or hemodynamic monitoring (non-dialysis central venous access, NDCVA).

There is strong scientific evidence that DCVA should be locked with an anticoagulant solution, so to prevent the risk of lumen occlusion due to clots: this is true for any dialysis catheter, either non-tunneled or cuffed-tunneled, either inserted in the cervico-thoracic area (internal jugular vein, innominate vein, etc.) or in the groin (femoral vein). The lock solutions typically used for this purpose contain either heparin or sodium citrate, while some controversies still exist about the optimal concentration of anticoagulant (ranging from 500 to 5000 units/mL in the case of heparin and from 4% to 40% for citrate). Citrate lock is currently used in many European hospitals as an effective strategy for preventing lumen occlusion of dialysis catheters as well as for preventing the risk of infection due intraluminal contamination of the line; in fact, citrate has relevant anti-biofilm and anti-bacterial effects, which heparin has not. Also, dialysis catheters are sometimes locked with combined solutions including both citrate and taurolidine (another drug with antibacterial activity).

On the other hand, the evidence supporting the use of anticoagulant and/or antibacterial lock solutions is scarce in the area of NDCVA. There is no convincing evidence that specific lock solutions might have clinical advantage over saline in preventing lumen occlusion of short-term, medium-term or long-term central venous access devices such as non-tunneled centrally inserted central catheters (CICC), peripherally inserted central catheters (PICC), femorally inserted central catheters (FICC), totally implantable venous devices (port) or long-term cuffed-tunneled central catheters. Though some guidelines (2, 3) have recommended the use of heparin lock for medium and long-term venous access devices (PICC, ports, cuffed-tunneled catheters) which are not in use, such recommendations were not based on convincing clinical evidence. Also, some specific lock solutions (citrate, taurolidine, ethanol, antibiotics, etc.) have been proposed not for preventing lumen occlusion but for reducing the risk of catheter-colonization or catheter-related blood stream infection (CRBSI); though, obviously, prevention of infection is mainly based on bundles of interventions which should be adopted during central line insertion and during the care of the exit site (1, 2), still it is believed that some kind of antibacterial lock might be effective in reducing the risk of intraluminal bacterial contamination of the device, particularly in high-risk patients. The data available from the literature are still not conclusive and no recommendation is offered by most guidelines.

The aim of this consensus is to review systematically the evidence for the choice and clinical use of the most appropriate lock solutions for central venous catheters not used for dialysis or apheresis, so to provide an evidence-based set of recommendations for the current clinical practice as well as for future research in this field.

Methods

There are several guidelines and statements addressing the issue of the most appropriate lock solution for non-dialysis central venous access (NDCVA), but most of them are based on poor-quality evidence, since only few randomized clinical trials are available in this area. On the other hand, retrospective and prospective studies, reviews and meta-analyses focused on this aspect of clinical practice have led to controversial conclusions; as a result, protocols of lock therapy for NDCVA are quite divergent and often based on personal preference or historical tradition.

Considering the nature of the problem and the scarcity of strong evidence from high quality scientific studies, a consensus was considered the most appropriate tool for providing recommendations in this area.

This consensus was developed by GAVeCeLT – the Italian Group of Long Term Venous Access Devices. A panel of experts was chosen, consisting of eight voting panelists, one independent chairperson with expertise in consensus methodology (ML), and one non-voting observer (EDL). Panelists were selected for their expertise in central venous access devices and/or as authors of relevant papers published on this topic. The meeting was not sponsored directly or indirectly by any commercial company, but exclusively supported by GAVeCeLT. It was conducted in two stages, both with formal and web-based meetings. Before the formulation of the statements to be discussed by the panel, a literature search was performed, with the assistance of the methodologist, on all English language articles from 1999 to 2014 reported in PubMed, Embase and Ovid, using specific terms and MeSH headings as "central venous catheter", "lock", "thrombosis", "infection", "antibiotic", "complication", "anticoagulant", "normal saline", "complications", and many others. Only human clinical studies on lock solutions of NDCVA were considered, regardless of the endpoints (prevention of occlusion

and/or prevention of infection). Both studies in adults and in pediatric patients were included. Papers on lock solutions for peripheral venous access devices (PVAs) and central venous access catheters for dialysis (DCVA) were not considered. Also, studies on lock solutions for treatment of occlusion and/or of infection were excluded by the analysis, the focus being exclusively on prevention.

The consensus process was carried out according to the formal RAND/University of California at Los Angeles (UCLA) Appropriateness Methodology as a two-stage consensus process (4). The method is a modification of the Delphi method, a structured process for collecting and condensing knowledge from a group of experts through a series of questionnaires. The RAND/UCLA method was originally used to assist in determining the relative weight of benefits and arms of medical progress (5) but has also been used to develop other medical guidelines and recommendations (6, 7). A list of issues and statements was defined and all participants were asked to independently score these statements using a 9-point Likert scale on a scale ranging from 1 (strongly disagree) to 9 (strongly agree). After this initial assessment, during a formal face-to-face meeting, the whole panel discussed the results of a first questionnaire. A second questionnaire was developed, including new issues identified during the first round. The results of the second questionnaire were customized and presented to the panel for final approval. Agreement levels (disagree, uncertain, agree) for each statement were calculated as the median panel score. A median of 1-3 indicated disagreement with the statement; 4-6, uncertainty; and 7-9, agreement. The level of consensus for each statement (inter-panel score variation) was calculated by the Inter-Percentile Range Adjusted for Symmetry (IPRAS) method (4). An IPRAS score >0 indicates consensus among the group, with higher scores indicating a stronger consensus level. Only statements reaching agreement or disagreement were included in these recommendations. After the conference, the recommendations and summary of the consensus was circulated to the panel for review and final approval.

The results are presented as statements stemming from the following seven main questions discussed by the panel:

1. Is there a role for anticoagulant lock in the management of non-dialysis central venous access (NDCVA), as a method for prevention of lumen occlusion?
2. Which drug (heparin, citrate, urokinase, recombinant tissue plasminogen activator [r-TPA], etc.) may have a primary role in this kind of lock?
3. Is there evidence that lock with normal saline might be as appropriate as an anticoagulant lock, in terms of prevention of lumen occlusion?
4. Is there any evidence about the most appropriate flushing method with saline before any kind of lock?
5. Is there a role for antimicrobial agents in the lock of NDCVA, as a method for prevention of catheter colonization or catheter-related blood stream infection?
6. Which antimicrobial agents (antibiotics, citrate, taurolidine, ethanol, ethylene-diamine-tetra-acetic acid [EDTA], etc.) may have a primary role in this regard?
7. Is there any anticoagulant/antimicrobial association that may have a role for the lock of NDCVA?

Results

Q1 – Is there a role for anticoagulant lock in the management of non-dialysis central venous access (NDCVA), as a method for prevention of lumen occlusion?

Lumen occlusion is a serious concern with any kind of central venous access device; it represents one of the more frequent adverse events leading to CVA failure. Prophylactic strategies to prevent this complication are mainly based on the use of standardized protocols for flushing and locking CVA in the interval between infusions. The use of anticoagulant lock to prevent occlusion of NDCVA has traditionally been used in the past, on the basis of a legitimate suspicion of effectiveness; it was initially described back in the 1970s, with little or no evidence, mainly inferred by the experience with DCVA. Since then, many different locking protocols have been described with the use of a heterogeneous variety of heparin concentrations.

The process of "in vivo" catheter occlusion is complex and multifactorial, not simply based on blood clotting and/or deposit of blood proteins or blood cells: in fact, the intraluminal occlusion is often secondary to the simultaneous deposit of remnants of therapeutic solutions (drug precipitates, contrast media, blood-derived products, lipids of parenteral nutrition, etc.) interacting with bacteria-derived biofilm and bacterial debris. Thus, even from the theoretical point of view, there are few chances that heparin lock may be really effective, as it would act only on the blood-derived portion of the material present inside the lumen; furthermore, it would surely be ineffective when a consistent blood reflux occurs in the system. This may explain the absence of evidence of efficacy of heparin solution in preventing lumen occlusion in NDCVA, as testified by the current literature. Also, there is no evidence that the efficacy of the heparin lock might be dose or concentration dependent. On the other hand, the adoption of heparin or other anticoagulant drugs may increase the risk of undesired side effects and/or severe iatrogenic complications (8-14). The risk of occlusion is currently considered to be related to inappropriate policies of flushing and/or inappropriate use of the line so to allow blood reflux into the device (typically: inappropriate use of needle-free connectors); most guidelines recommend the use of needle-free connectors with neutral or positive displacement, adoption of a 'no-reflux' strategy, avoidance of simultaneous infusion of incompatible drugs and appropriate flushing with saline before and after each infusion (see below), while there is no evidence that valved CVA may reduce the risk of occlusion (15, 16).

In the last two decades, several studies have shown that normal saline is a safe and effective alternative option to heparin lock in peripheral vascular access devices (PVA) and in CVA used for pediatric patients (17-20). Similar results have been reported for medium and long-term NDCVA in adults (21). In particular, a recent randomized controlled trial supports the conclusion that normal saline is the best choice as a locking solution for ports, if combined with a strict adherence to a protocol for device insertion and maintenance (22).

Other anticoagulant lock solutions (trisodium citrate at different concentrations, thrombin inhibitors, fibrinolytic drugs and plasmin activators), have been reported to have

similar efficacy in preventing occlusion compared to heparin in NDCVA (23, 24). Although, they have never been compared to normal saline. In particular, no study has ever tested the efficacy of citrate versus saline in the prevention of lumen occlusion of NDCVA. Such studies might be particularly desirable in selected categories of patients with NDCVA at high risk of infection, considering the potential role of citrate in decreasing intraluminal bacterial contamination.

Panel recommendation

The role of anticoagulant lock is only marginally important in the management of NDCVA, in terms of prevention of lumen occlusion.

Future assessment of the role of citrate lock in NDCVA is desirable and considered to be of increasing importance. The benefit of citrate might be more focused on its action against biofilm and against bacteria rather than on its anticoagulant effect.

Q2 – Which drug (heparin, citrate, urokinase, rTPA, etc.) may have a primary role in this kind of lock?

Five different anticoagulant agents were considered: heparin, urokinase, trisodium citrate, r-TPA, EDTA.

There are relevant clinical studies to support the anticoagulant efficacy of heparin or citrate, for locking purposes, specifically in DCVA. The guidelines of the Infusion Nursing Society (INS) – in the recently published 2016 edition – recommend to lock all DCVA with heparin (1000 units/mL in VAD for dialysis, 100 units/mL in VAD for apheresis) or 4% citrate (1). As suggested by the American Society of Diagnostic and Interventional Nephrology (ASDIN) (25), the use of 4% citrate lock appears to be a safe alternative to 1000 units/mL heparin lock in DCVA. A recent meta-analysis of 13 randomized controlled trials suggested that citrate locks are superior to heparin locks in preventing CRBSI in patients with DCVA (risk ratio [RR]: 0.39, $p<0.001$) (26). Citrate locks were also associated with significantly lower risk of bleeding events compared to heparin locks in this patient population (RR: 0.48, $p = 0.002$), while outcomes regarding catheter patency were comparable. In a 2010 position statement on the management of DCVA, the European Renal Best Practice (ERBP) supported citrate 4% to prevent CRBSI (27). In addition to its anticoagulant properties, citrate has the advantage of antimicrobial activity and reduction of biofilm formation (28). Available solutions of citrate have concentrations ranging from 4% to 46%: the efficacy on preventing lumen occlusion appears to be dose related, as higher concentrations yield better results. The effects of citrate are secondary to its calcium-chelating properties, which accounts for both the antimicrobial and the anticoagulant effect. The decreased risk of bleeding events is likely to be secondary to the rapid metabolism of citrate in the bloodstream. This latter property is important in the event of the citrate-containing lock being inadvertently flushed into the systemic circulation.

Nevertheless, citrate formulations have met safety concerns. High citrate concentrations must be used cautiously because of potential adverse effect such as peripheral paresthesia, metallic taste and even serious arrhythmias (29, 30). In 2000, the FDA recommended against use of high concentration citrate (46.7%) as a catheter anticoagulant, due to a case report of a patient who experienced cardiac arrest, possibly secondary to hypocalcemia, following a full-strength injection into a newly placed hemodialysis catheter. Additional serious adverse effects associated with high concentrations of citrate lock solutions continue to be reported worldwide, and the FDA currently recommends citrate concentrations of no more than 4% for use as catheter lock. The ERBP also recommends 4% citrate solution, which is associated with a preferable benefit/risk ratio if compared to higher concentrations. Some citrate solutions at high concentration may be indicated for use in apheresis procedures.

These clinical advantages of citrate in DCVA have sparked an increasing interest for citrate use also in NDCVA, especially considering the simultaneous efficacy on the maintenance of patency and potential reduction of CRBSI. While the increasing attention among researchers on its use for NDCVAs is justified, the main problem appears to balance the efficacy and safety of the different solutions currently available.

Conversely, there is scant literature evidence on the use of fibrinolytics and r-TPA in preventing catheter occlusion. When adopted as anticoagulant lock in DCVA, they were less effective than heparin or citrate, being markedly more expensive and more likely to be associated with undesired effects or hemorrhagic complications. Given these limitations, in the case of NDCVA, their clinical use should be limited to the treatment of occlusion and not to its prevention (31): they will be obviously indicated only for the treatment of occlusion secondary to blood clots, since occlusions due to drug precipitates, contrast medium or lipid aggregates will not be affected by fibrinolytics. Regarding urokinase, most reports deal with its use in treating clot-related malfunction, especially in hemodialysis patients, more than lock treatment. Declotting can be done with “high-dose” or “low-dose”, but no consensus exists on the adequate dose to obtain thrombolysis (32). Again, the vast majority of available evidence comes from the DCVA clinical setting, and more studies are needed to clarify the cost effectiveness of thrombolytic agents in preventing catheter clotting and catheter-related bacteremia in NDCVA. The recent INS guidelines suggest the use of r-TPA to lock DCVA once per week as a strategy to reduce CRBSI (1).

Finally, there are scarce clinical data regarding the use of EDTA in catheter locks (mainly as preventive tool), but the preliminary results are promising, and further investigations addressing this topic are required, considering the specific action of EDTA against biofilm.

Panel recommendation

Heparin lock and citrate lock both guarantee an effective anticoagulant action, which is proven to be useful in DCVA rather than in NDCVA.

Thrombolytic/fibrinolytic drugs, as currently available, are neither safe nor cost effective for prevention of occlusion of NDCVA, while they have a definite role in the treatment of lumen occlusion due to blood clots.

Q3 – Is there evidence that lock with normal saline might be as appropriate as an anticoagulant lock, in terms of prevention of lumen occlusion?

When using heparin lock, several pharmacological and clinical issues must be taken in account. Heparin by itself is not a thrombolytic substance and it does not actively cause the lysis of the intraluminal blood clot; it merely prevents the progression of the obstruction by inhibiting further clot formation and allowing the activation of natural clot lysis. Moreover, heparin has a very short half-life, from 60 to 90 minutes, and there is no evidence of the persistence of its efficacy inside the catheter for longer times.

Heparin has also relevant side effects: it may be associated to drug hypersensitivity, drug incompatibilities and cause heparin-induced thrombocytopenia, especially in dialysis and cancer patient, where serious or life-threatening complications may occur. Errors in the dosage or in the concentration may be associated with iatrogenic hemorrhages, suggesting the opportunity of labeling heparin vials as a "high alert medication" (14). In addition, episodes of CRBSI due to contamination of heparinized solution have been reported (33, 34), especially when the heparin solution is not properly manipulated.

The possibility of using a saline lock rather than a heparin lock has been extensively investigated since the 1990s in particular for pediatric patients, PVA and/or short- or medium-term CVA. The majority of these reports failed to show a superiority of heparin when compared to saline in preventing catheter malfunction or failure for occlusive events. Moreover, the routine use of a normal saline lock was not shown to increase the incidence of infective complications (18-20, 35): this was an expected finding, considering that heparin has no antibacterial activity.

Since then, catheter lock with normal saline (i.e., preservative-free 0.9% sodium chloride) has been used for many types of medium- and long-term CVA. Recent trials have demonstrated the non-inferiority of saline versus heparin and its efficacy in preventing occlusion in ports and PICCs (21, 22, 36).

The recent standards released by INS (1) conclude that since randomized controlled trials have shown equivalent outcomes with heparin and saline lock solutions for CICCs, PICCs and ports, there is insufficient evidence to recommend one lock solution over the other. The same guidelines recommend saline lock for peripheral VAD in adults, but do not offer strong recommendations in neonates and children, considering that evidence on the preference of saline versus heparin for peripheral VADs is controversial in these patient populations (1). Interestingly, the 2016 INS guidelines recommend that the volume of saline for flushing should be at least twice the internal volume of the system (catheter plus add-on devices), while the volume of saline lock should be at least the internal volume plus 20%.

In conclusion, there is wide convergence to state that lock with normal saline solution is as appropriate as lock with anticoagulants in terms of prevention of lumen occlusion in NDCVA. The panel considered this statement to be valid for any type of NDCVA (short-term CICCs and FICCs, PICCs, cuffed-tunneled catheters, ports), in all population of patients (both adults and pediatrics).

Panel recommendation

Saline lock is as appropriate as anticoagulant lock in prevention of occlusion of NDCVA.

Q4 – Is there any evidence about the most appropriate flushing method with saline before any kind of lock?

Flushing is of primary importance to achieve a correct intraluminal cleansing, in any peripheral venous access (PVA), as well as in any NDCVA (tunneled and non-tunneled CICCs, PICCs, ports, etc.). There is an increasing attention to procedures and technology developments concerning this maneuver. Relevant issues are timing, type of solution, volumes, pressure and technique of flushing.

Most international recommendations state that flushing should be performed before and after the administration of any kind of intravenous infusion (so-called 'SAS' sequence, i.e., Saline-Administration-Saline) and before and after blood sampling. For flushing purposes, normal saline (0.9% NaCl) is the recommended solution for any kind of device in standard clinical practice. A volume of 10 mL is generally considered to be sufficient for the majority of adult patients with NDCVA, so to guarantee the removal of most intraluminal deposits of drug precipitates (3, 21, 37, 38). Volumes higher than 10 mL (typically: 20 mL of normal saline) should be flushed in adult patients after the infusion of viscous solutions (radiologic contrast media, blood products, lipid-based parenteral nutrition) (39); although, there is a lack of clinical studies supporting the major efficacy of this approach. In CVA of pediatric patients, lower volumes are used (5 mL for standard flushing and 10 mL to clear viscous solutions). In adult patients, 5 ml flushing of PVA is usually recommended. The recently published INS Standards recommend that the flushing volume should not be inferior to the double of the priming volume of the line to be flushed (i.e., also including possible extensions) (1).

The technique of flushing is generally considered to be relevant to obtain a correct cleansing of the catheter lumen. Flushing should be carried out by hand-operated syringe, since gravity infusions or pump-driven infusions are not effective in this regard. When flushing silicone catheters and/or non-power-injectable devices, 10 mL volume syringes are recommended, so to prevent pressure damage to the catheter (3, 37, 40). Continuous hand-operated infusion of 10 mL saline appears to be less effective than dynamic pulsatile infusion (the so-called "push and pause" or "start and stop" method), as the latter creates turbulence inside the catheter: such maneuver is widely recommended in the literature and in most international guidelines (3, 22, 37, 39-41). In vitro studies on the dynamic flush efficacy of the discontinuous flow infusion demonstrated its superiority in preventing the intraluminal deposit of substances if compared to continuous laminar flow infusion (42). In the literature, few studies on flushing hydrodynamics have been provided (43), and there is limited evidence of the antimicrobial efficacy of the pulsatile flushing technique for catheters (44). However, based on the potential advantages of dynamic flush and the absence of side effects of the technique, its use is widely recommended for all flushing procedures and in particular for any kind of CVA. It is important that the 'pause' phase during the 'push

and pause' maneuver should not be associated with an accidental blood reflux due to a back movement of the piston of the syringe.

For long-term CVAs that are not in use, the most popular interval timing for flushing is 2 weeks (for tunneled-cuffed CVAs) or 4-6 weeks (for totally implantable ports). A 3-day or 7-day interval has been suggested for PICCs (38). However, there is scant evidence in literature about the ideal interval in terms of efficacy in maintaining patency and it is quite likely that longer intervals may be adopted. As recommended by HICPAC guidelines, a proper aseptic technique during CVA flushing is an important aspect of bundle strategy to prevent CLABSI (37).

There are some literature evidences on the efficacy of the use of prefilled syringes versus manually filled syringes to reduce manipulations and thus the risk of infection (45, 46). The recently published INS Standards (1) recommend using single-dose systems (e.g., single-dose vials or prefilled labeled syringes) for all VAD flushing and locking. In addition, some prefilled saline syringes are specially designed to guarantee the maintenance of a positive pressure at the end of the infusion, thus preventing back-flow of blood into the catheter. Further clinical trials are advisable to support a widespread use of these syringes, which may play an important role in a maintenance policy adopting a 'no-reflux' strategy.

Panel recommendation

A pulsatile positive "push and pause" ("start and stop") technique is the most appropriate methodology of flushing.

Q5 – Is there a role for antimicrobial agents in the lock of NDCVA, as a method for prevention of catheter colonization or catheter-related blood stream infection?

Colonization of a vascular catheter is the first step of infection. Catheters are mainly colonized via the extra-luminal or by the intra-luminal route (47). For short-term CVAs (mean duration <7-10 days), the skin around the catheter insertion site is the most common source of microorganisms (48, 49): skin flora migrates along the external side of the catheter, into the subcutaneous tract (so called 'extra-luminal colonization'). For medium- and long-term CVA, contaminated catheter hubs are the most common source of entrance of microorganisms, by migration via the internal surface of the catheter ('intra-luminal colonization') (50, 51).

Bacteria and fungi colonize PVA and CVA in a clustered form, creating aggregates of cells (biofilm). A microbial biofilm is "a structured consortium of microbial cells surrounded by a self-produced polymer matrix" (52). In addition to bacteria and fungi, the biofilm matrix also includes components from the host (fibrin, platelets, immune-globulins, etc.). Biofilms can be mono- or poly-microbial (52-55).

Biofilm may favor chronic infections, since it shields bacteria from the exposure to antibiotic drugs and to the host's antibodies and macrophages, so that the infection may persist despite adequate antibiotic therapy and despite the host's defense mechanisms. Antibiotic failure during CRBSI treatments is often due to persistence of germs inside the biofilm. In such cases, catheter removal is considered the best choice of treatment (56).

In some cases, catheter salvage could be a highly desirable option, particularly in patients with limited availability of veins for new venous accesses and/or with high risk of infection, such as onco-hematological patients or patients receiving parenteral nutrition (57, 58).

If *Staphylococcus aureus* or *Candida spp*. are involved as etiologic agents, catheter removal is the first option, while conservative treatment may be adopted when CRBSI is due to other microorganisms such as coagulase-negative Staphylococci and Gram-negative bacilli (57, 58). When trying to save the device, the best option is the combination of systemic antibiotics plus antimicrobial lock therapy.

The antibiotic lock technique was first described almost 30 years ago for the treatment of catheter-related sepsis without a tunnel or exit site infection and without metastatic complications in tunneled catheters, in home parenteral nutrition patients (59). Antibiotic lock technique consists in administrating an antibiotic solution into the hub and into the lumen of a CVA that is not in use, so to achieve a very high concentration, far higher than the minimal inhibitory concentration for the bacteria involved (2, 60). The antibiotic solution must remain in the lumen for a long period of time (from hours to days). Such strategy is often very effective, especially (a) if the antibiotic solution stays inside the lumen for a long period, (b) if the germs are CONS (up to 100% of success) or Gram-negative (up to 75% of success), and (c) if the lock is associated with the systemic administration of antibiotics. Systemic antibiotic administration without lock is much less effective: in 14 open trials dealing with salvage of long-term catheters by administration of standard parenteral therapy only, the mean success rate in treating CRBSI was 67%; this probably reflects the inability of most antibiotics to achieve therapeutic concentrations when microorganisms are clustered inside the biofilm (61-66). The antimicrobial lock technique is recommended by current guidelines as a part of management of catheter-related infections in a few well-defined circumstances (not complicated, non-metastatic infections, when the salvage of catheter is highly required) (56).

On the other hand, the use of antimicrobial lock solutions as a prophylaxis of infection is much more controversial. Over the past years, several randomized trials have addressed this issue, with encouraging results (67, 68). However, concerns still exist about the possible emergence of antimicrobial-resistant bacteria (69) and about the risk of non-infective complications (70); also, some studies have suggested that antimicrobial lock prophylaxis may have little or no advantages if compared to standard prevention strategies such as appropriate maintenance bundles (71). Therefore, antimicrobial lock prophylaxis is not recommended as a routine technique to prevent catheter-related infections (2, 72, 73).

Centers for Disease Control and Prevention (CDC) guidelines recommend antimicrobial lock solutions to prevent CRBSI only in few special circumstances (patients with long-term CVA, or patients with a history of multiple CRBSI in spite of adherence to strict aseptic techniques) (2).

According to the SHEA/IDSA guidelines (73) antimicrobial lock solutions should not be used routinely to prevent

catheter-related bloodstream infections in NDCVA, for several reasons: (a) because the majority of the studies on this issue have been conducted in hemodialysis patients and therefore cannot be generalized; (b) because the scientific evidence for the effectiveness of the routine use of antibiotic-based lock solutions is weak (73) and (c) because of the concern that the use of such solutions may increase the antimicrobial resistance (2).

As a matter of fact, considering the risk of antimicrobial resistance, the SHEA/IDSA guidelines (73) suggest to use antibiotic lock solutions as a preventive strategy only in few situations: (a) patients with long-term hemodialysis catheters; (b) patients with limited venous access and a history of recurrent central line-associated blood stream infection (CLABSI); (c) patients who are at heightened risk of severe sequelae from a CLABSI (e.g., patient with recently implanted intravascular devices, such as prosthetic heart valve or aortic graft). A similar conclusion is offered by the recent INS guidelines (1), which suggest the use of antimicrobial locking solutions for infection prevention in patients with long-term NDCVAs, in patients with a history of multiple CRBSI, in high-risk patient populations, and in facilities with unacceptably high rates CLABSI, despite application of other methods of infection prevention. In that same document, many possible antimicrobial solutions are taken into consideration, such as antibiotic lock solutions contain supratherapeutic concentrations of antibiotics, or antiseptic locking solutions (ethanol, taurolidine, citrate, 26% sodium chloride, methylene blue, fusidic acid, or EDTA) (1).

According to the conclusions of a very recent meta-analysis (74) of randomized controlled trials on antimicrobial lock solutions as a method to prevent CLABSI, "use of antimicrobial lock solutions is an effective prevention strategy to reduce the risk of CVC infections. Although the limited number of prospective, randomized studies in pediatric and hematology patients may preclude an imminent change in policy in these subgroups before larger trials are performed, existing evidence in patients receiving hemodialysis suggests that implementation of antimicrobial lock prophylaxis should be considered".

Furthermore, it is possible that the use of antimicrobial lock solutions which do not contain antibiotics may eliminate the risk of antimicrobial resistance and find a role in the future clinical practice.

Panel recommendation

While antibacterial lock (specifically with antibiotics) has a clear role in clinical practice as a treatment of some selected CRBSIs, the use of antibacterial lock for the purpose of prevention of catheter colonization and/or infection is a new field which demands further research, as it may prove to have an important clinical role in some selected populations of high-risk patients where the standard bundles of infection prevention appear to be ineffective or insufficient.

Q6 – Which antimicrobial agents (antibiotics, citrate, taurolidine, ethanol, ethylene-diamine-tetra-acetic acid [EDTA], etc.) may have a primary role in this regard?

This question was mainly addressed for five different types of antibacterial agents: antibiotics, taurolidine, citrate, ethanol, EDTA. Considering the risk of allergy reactions and the potential emergence of bacterial resistance, antibacterial lock with antibiotic drugs may not be regarded as an interesting area of development in the future, while the use of non-antibiotic lock solutions will attract more interest.

The role of citrate lock has been discussed above (question 2 to the panel). Other non-antibiotic lock solutions include taurolidine, ethanol and chelating agents (sodium citrate, EDTA).

Taurolidine, a derivative of the amino acid taurine, is an antimicrobial agent with a broad spectrum activity against bacteria and fungi. The methyl derivatives interact with bacterial cell wall causing an irreversible injury. Resistance to taurolidine has never been reported at this time (75). Several studies on the effect of taurolidine in preventing CRBSI have been published (75-87). A meta-analysis on some of these studies (88) found that the use of taurolidine was associated with a reduced CRBSI rate compared to other control lock solutions, also in high-risk patients. Moreover, as already mentioned, resistance to taurolidine is apparently absent, probably because this drug acts as a biocide and not as an antibiotic (89). This is really an important issue, that allows overcoming the concern of potential antimicrobial resistance induced by antibiotic lock solutions. The usual concentrations of taurolidine (1.35%-2%) are at least 10 times higher of the MIC_{50} of the majority of Gram-positive and Gram-negative microorganisms, without significant differences between the two (90).

Moreover, no adverse effects have ever been reported with the use of taurolidine. At this time, studies are needed to clarify the appropriate indication of taurolidine (one possible indication being, for example, recurrent episodes of CRBSI in patients on home parenteral nutrition despite a good adherence to hand washing, aseptic technique, etc.) and its cost effectiveness (90).

Ethanol lock solutions can also reduce the risk of CRBSI, as proven mostly in pediatric patients and in the setting of parenteral nutrition. A recent report from Tan et al (91) evaluated 13 ethanol lock prophylaxis studies and 617 patients. All studies reported decreased rates of infection and of catheter removal. The most effective ethanol concentration was 70%. In the same paper, nine studies of ethanol treatment were also evaluated. Ethanol lock was actually effective also as a treatment of CRBSI, with 90% cure and 84% line salvage, when associated with systemic administration of antibiotics. Still, there are some concerns about safety of ethanol. Abu-El-Haija et al (92) found a reduction of infection rate but also a negative effect of ethanol on catheter integrity. Mermel and Alang (93) found that the use of ethanol lock may be associated with structural changes in catheters (mostly standard polyurethane, but also silicone and carbothane catheters) and with increased risk of catheter occlusion and of systemic toxicity (e.g., abnormalities of liver function test). Further studies are needed to clarify the potential negative effects of ethanol on patients and vascular devices.

Chelating agents (sodium citrate, EDTA) are also promising as non-antibiotic antimicrobial lock solutions to prevent CRBSI, alone or with other substances (e.g., taurolidine). A few studies suggest their effectiveness. They might have some advantages over antibiotic locks: no reported bacterial resistance, low industrial costs, ability to prevent catheter occlusion.

Panel recommendation

Non-antibiotic antibacterial lock will have a major future role for prevention of catheter colonization and infection. While ethanol lock is highly effective, due to concerns about its safety, the drugs most likely to be used as antibacterial lock are taurolidine and citrate, which have optimal characteristics in terms of safety, efficacy and cost effectiveness.

Q7 – Is there any anticoagulant/antimicrobial association that may have a role for the lock of NDCVA?

Among the antimicrobial-anticoagulant associations that appear to be useful for the lock of NDCVA, probably the most effective and promising is taurolidine-citrate.

It has been shown that this combination is effective (and more effective than heparin alone or than the combination taurolidine-heparin) in preventing both CRBSI and catheter occlusion in patients with cancer and in parenteral nutrition, as well as in hemodialysis.

Since 2002, Shah et al (75) reported the high activity of taurolidine-citrate lock against planktonic microbes, a relevant antimicrobial activity in a catheter model and a significant eradication of biofilm. Simon et al (76) in a single-center prospective pediatric 48-month cohort study, compared patients receiving chemotherapy in 2003-2005 (heparin lock) and in 2005-2007 (taurolidine-citrate lock). In the latter group, the use of taurolidine-citrate significantly reduced CRBSI. In a population of pediatric patients with hematological malignancies, taurolidine-citrate has been shown to be superior to heparin (82). A meta-analysis from Liu et al (90) showed that taurolidine-citrate is effective in preventing CRBSI, although the risk of catheter occlusion may also be increased. In this exploratory meta-analysis, three studies involving 236 patients with a total of 34,984 catheter days were included. The use of taurolidine-citrate significantly reduced the risk of CRBSI (RR = 0.47, 95% CI: 0.25-0.89) and of Gram-negative bacterial infection. There was no significant difference in Gram-positive infections and exit-site infections.

In the future, further studies are needed to identify the most appropriate concentrations of taurolidine (actually 1.35%-2%) and of citrate (actually 4%) to prevent both infection and occlusion.

Panel recommendation

The association that is most promising as antibacterial/anticoagulant lock, in NDCVA as in DCVA, is taurolidine-citrate.

Further studies should clarify which populations of patients might benefit from this association, and which concentrations of taurolidine and of citrate might be associated with the best outcome in terms of safety and efficacy.

Conclusions and call for further research

The role of lock in preventing occlusion of NDCVA

This panel has stressed the limited value of available evidence supporting the use of heparin as a locking agent in NDCVA. Although heparin lock has been used for years in NDCVA – especially in totally implantable venous access devices – it is now evident that it is not superior to saline lock for the prevention of lumen occlusion and/or catheter colonization and/or catheter-related blood stream infections (CRBSI).

The maintenance of the patency of NDCVA appears to be mainly based on other factors, such as an appropriate flushing policy including the manual pulsatile flush technique, the adoption of needle-free connectors with positive or neutral displacement, a 'no-reflux' strategy which may include no-reflux syringes and closure of the system maintaining an inner positive pressure, and – last but not least – an appropriate education of the staff caring for the central line.

Obviously, further research is needed, as a single randomized controlled trial may not allow for a meta-analysis and definitive conclusions, and most publications are either case-control or cohort studies, which may affect the quality of the evidence provided. Therefore, it may still be difficult to provide high-quality recommendations for schedule and frequency of saline lock in the different types of devices and in different clinical settings.

Still, the routine use of heparin lock in NDCVA should be strongly questioned, considering the lack of evidence of efficacy and its potential costs and risks, as compared with saline, which is absolutely safe.

Furthermore this panel has stressed the need for rigorously designed, high-quality randomized controlled trials and biological studies addressing other agents (such as citrate) and other end-points (antimicrobial effect), so to provide more definitive and precise evidence of efficacy for translation to clinical practice. Citrate has been proposed by the panelists as a very promising agent to be investigated in the near future, basing this position mainly on findings from DCVA.

Panel has agreed that there is sufficient evidence to support the use of normal saline as locking agent for preventing lumen occlusion, in short-term as well as in mid- and long-term catheters not used for dialysis or apheresis. Future research should be focused on administration schedule and frequency of normal saline lock, and on possible impacting factors such as different flushing methods.

Flushing technique is judged of paramount importance. 'Push-pause' (or 'start-stop') method is the most recommended, especially with PICC and long-term CVA, where significant time intervals between each use may occur.

Panelists have strongly suggested that more studies on hydrodynamics of flushing techniques should be carried out, as proper flushing is critical for removing proteins, cells and debris from the lumen of the catheter. Finally, use of prefilled syringes and precise definition of time intervals have been confirmed as hot issues for future research.

The role of lock in preventing infection of NDCVA

The panel considered this a very important issue, claiming further investigation. While overall CRBSI rates appear to have decreased in the last 10-15 years, they remain a substantial

TABLE I - Panel recommendations

The role of lock in preventing occlusion of NDCVA
The role of anticoagulant lock is only marginally important in the management of NDCVA, in terms of prevention of lumen occlusion.
Future assessment of the role of citrate lock in NDCVA is desirable and considered of increasing importance. The benefit of citrate might be more focused on its action against biofilm and against bacteria rather than on its anticoagulant effect.
Heparin lock and citrate lock both guarantee an effective anticoagulant action, which is proven to be useful in DCVA rather than in NDCVA.
Trombolytic/fibrinolytic drugs, as currently available, are neither safe nor cost-effective for prevention of occlusion of NDCVA, while they have a definite role in the treatment of lumen occlusion due to blood clots.
Saline lock is as appropriate as anticoagulant lock in prevention of occlusion of NDCVA.
A pulsatile positive "push and pause" ("start and stop") technique is the most appropriate methodology of flushing.
The role of lock in preventing infection of NDCVA
While antibacterial lock (specifically with antibiotics) has a clear role in clinical practice as a treatment of some selected catheter-related blood stream infection, the use of antibacterial lock for the purpose of prevention of catheter colonization and/or infection is a new field which demands further research, as it may prove to have an important clinical role in some selected populations of high risk patients where the standard bundles of infection prevention appear to be ineffective or insufficient.
Non-antibiotic antibacterial lock will have a major future role for prevention of catheter colonization and infection. While ethanol lock is highly effective, due to concerns about its safety, the drugs most likely to be used as antibacterial lock are taurolidine and citrate, which have optimal characteristics in terms of safety, efficacy and cost-effectiveness.
The association that is most promising as antibacterial/anticoagulant lock, in NDCVA as in DCVA, is taurolidine/citrate. Further studies should clarify which populations of patients might benefit of this association, and which concentrations of taurolidine and of citrate might be associated with the best outcome in terms of safety and efficacy.

source of morbidity and mortality in any health-care system. Guidelines from the Centers for Disease Control and Prevention (2) recommend antimicrobial lock of NDCVA as prophylaxis for patients with long-term catheters and history of multiple CRBSI despite maximal efforts to follow aseptic techniques. The exact mechanisms of antibiotic resistance within biofilm remain unclear, yet a common hypothesis is sub-therapeutic exposure of biofilm cells to antibiotics. Use of antibiotics is still a critical issue, as low-level exposure of antibiotics may potentially increase the risk of bacterial resistance. Availability of new, more effective and safer drugs might change this scenario in the near future, claiming efficacy and cost/effectiveness evidence.

Characteristics of the ideal antimicrobial lock solution are far from being reached. They include ability to penetrate or disrupt a biofilm, wide spectrum of activity, prolonged stability, low risk of toxicity and adverse events, low potential for bacterial resistance, as well as cost effectiveness. According to a recent systematic review and meta-analysis (94), ethanol, taurolidine and some antibiotics (daptomycin, tigecycline) appear to be the best current options as antibacterial lock for treating CRBSI, whereas evidence for antibacterial lock for infection prevention is still scarce.

Non-antibiotic antiseptics, such as ethanol, taurolidine and citrate, have been used in a lock solution for the prevention of CRBSI, with evidence of efficacy; although, all these agents require further research in order to define their safety and cost effectiveness in different populations with NDCVA.

According to the panel, citrate and taurolidine are the most promising agents to be investigated in the near future, due to their ability to penetrate a biofilm and to act against its cells (95).

The panel underscored the association of taurolidine-citrate lock solution as the main association to be further investigated.

Panel recommendations are reported in Table I.

Disclosures

Financial support: No grants or funding have been received for this study.
Conflict of interest: None of the authors has financial interest related to this study to disclose.

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