Central venous catheter-related bloodstream infections in children on maintenance haemodialysis: Prevention and treatment

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RESUMEN

Pese a las ventajas de la fístula arteriovenosa frente al catéter venoso central (CVC), por lo que respecta a menor incidencia de infecciones y trombosis, menos cambios de acceso y menos hospitalizaciones, hasta el 80 % de los accesos vasculares fueron CVC en diferentes series pediátricas debido a su sencillez para colocarlos, uso inmediato y ventajas de conexión sin aguja. Para disminuir las complicaciones relacionadas con el CVC y las revisiones/reemplazos posteriores, los CVC tunelizados deben tener unas dimensiones adecuadas al tamaño del paciente, siendo la vena yugular interna (primero la derecha y segundo la izquierda) las localizaciones preferidas. La bacteriemia relacionada con el catéter (BRC) sigue siendo una preocupación importante en muchas unidades de hemodiálisis pediátrica. Para disminuir las BRC, deben aplicarse medidas preventivas universales, un entorno estéril y una técnica aséptica cada vez que se manipula, conecta o desconecta un catéter venoso. Las soluciones de sellado antibiótico nunca deben sustituir a las normas higiénicas y las buenas prácticas clínicas en lo que se refiere al cuidado y la manipulación de los catéteres. Es esencial el manejo adecuado de las BRC con antibióticos sistémicos intravenosos basados en los resultados de sensibilidad de los cultivos y el sellado antibiótico adyuvante. No se recomienda la profilaxis rutinaria con una solución de sellado antibiótico, a menos que haya un riesgo muy elevado de BRC.

Palabras clave:

Hemodiálisis pediátrica, bacteriemia relacionada con el catéter, diagnóstico, tratamiento, sellado antibiótico.

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INTRODUCTION

In recent decades, the use of haemodialysis (HD) in children and adolescents has increased[1,2]. Well-functioning vascular access (VA) is the key to delivering optimal dialysis doses to patients, reducing VA-associated infectious and avoiding non-infectious complications. Available guidelines recommend the use of arteriovenous fistula (AVF) over a central venous catheter (CVC), whenever possible[3-5]. The second choice is arteriovenous graft (AVG), which is seldom used in children[6]. Although tunnelled CVC is the third choice VA for children receiving chronic HD, and there have been concerted efforts to increase the early establishment of AVF, recent studies show that CVC remains the first VA in a large proportion of children with end-stage kidney disease (ESKD)[2,6,7], even though they do not undergo consequent kidney transplantation (KTx) within a few months[2].

VASCULAR ACCESS CHOICES IN CHILDREN UNDERGOING CHRONIC HAEMODIALYSIS

Despite the suggested benefits of AVF over CVC, in terms of fewer infections, fewer access changes, and shorter hospitalisation periods[8], different paediatric series show that up to 80% of vascular accesses were CVC due to its advantages of immediate use and needle-free connection[1,6,7]. The use of AVF is more common in older children[7]. An ESPN/ERA-EDTA Registry report based on data from 18 European countries between 2000-2013 showed that 45% *vs.* 55% of paediatric HD patients require CVC *vs.* AVF, and children who received an AVF were significantly older when commencing HD[2]. Similarly, AVF was shown to be the predominant VA type in children over 15 years of age in Europe[7]. However, more recent data from the International Paediatric Haemodialysis Network (IPHN) Registry evaluating 552 children and adolescents on maintenance HD from 27 countries between 2012 and 2017 showed that CVCs were the leading VA (72%) at all ages[6]: only a quarter of

the children received AVF as the initial VA, and 2% had AVG. At 1 year only 2% had transferred to AVF and at 3 years this figure was 27%. Although the preference for a CVC in the paediatric population is explained in part by the technical difficulties associated with AVF placement in young children, CVCs were also the first choice for VA in 65% of patients older than 10 years[6].

COMPLICATIONS OF CVC

Of the 552 children included in the IPHN Registry, VA survival rates were consistently lower in years among CVC patients compared to AVF patients, with rates of 70% and 60% for CVCs and 92% and 83% with AVFs after 1 and 4 years of HD, respectively[6]. Vascular access dysfunction and the need for replacement were 2 and 3 times more common among children with CVC compared to AVF, respectively[6]. The top causes of VA revisions are CVC-related bacteraemia, CVC malfunction and thrombosis, AVF primary failure, and AVG dysfunction[9]. It is notable that IPHN only found infectious complications with CVCs (1.3/1,000 catheter days) and VA replacement was necessary in 47%[6]. In adults, CVC is associated with a risk of hospitalisation that is 2 times higher and an 8 times higher risk of VA infection[10].

CENTRAL VENOUS CATHETER LOCATION AND SIZE

In order to decrease CVC-related access complications and the subsequent revisions and replacements, CVC should be placed in an ideal location. The right internal jugular vein position, which provides a direct path into the superior vena cava, is the preferred location for insertion. This location is associated with fewer CVC-related infections and less dysfunction[6,9]. The left internal jugular vein is the second location. Subclavian vein stenosis is 4 times higher compared to the internal jugular vein, compromising the placement of AVF. Therefore, placement of a CVC in the subclavian vein should be avoided[6]. Even though subclavian catheters were used in 30-50% of patients according to the reports of earlier registries[1,11], recent IPHN data finds this use to be 14%[6]. In 628 permanent CVCs, 189 episodes of dysfunction were reported. Dysfunction was more frequent with CVCs placed in the femoral (56%) or subclavian vein (35%) compared to the internal jugular vein (21%). Catheter size is another important issue for the good functioning of VA in children and the best-fitting catheters based on patient size should be sought. Different formulas and methods have been proposed for calculating optimal CVC insertion length[12-14], however, they require validation.

Cuffed/tunnelled/permanent CVCs should be placed in patients on maintenance HD. Tunnelled HD-CVC with a Dacron cuff wraps around the tubing allows tissue integration to anchor the catheter inside the tunnel within 4 to 6 weeks, and protects against pericatheter bacterial entry into the bloodstream[9]. To improve blood flow, reduce recirculation, and mitigate the risk of catheter tip occlusion, many catheter designs have been evaluated but no differences in long-term functional outcomes related to catheter design were found (except the pre-formed split type in adults)[15].

HD CATHETER-RELATED INFECTIONS

Central catheter-related infections are associated with access revision and modality change, increased hospitalisation and mortality, complications that affect dialysis adequacy, decreased health-related quality of life, and implications for the economics of healthcare. Infectious complications were shown to be related to a 2 times higher risk of mortality and 8 times higher hospitalisation in adults on HD[10]. Two types of infectious episodes can be seen in HD patients. Infections can occur at the catheter exit site (ES) or inside the catheter itself. The latter will be called "catheter-related bloodstream infections (CRBSI)" in this review.

SOURCE AND RISK FACTORS OF CRBSI

Haemodialysis catheter microbial colonisation and biofilm formation typically arise in 3 ways:

1. Patient's own skin (exit site): Migration of microbial flora at the exit site onto portions of the extraluminal catheter surface that is tunnelled subcutaneously.
2. Healthcare providers' hands.
3. Catheter hubs: Contamination through an open HD catheter hub onto the intraluminal surface.

Direct seeding of the catheter due to bacteraemia episodes, old catheters, and surface erosion due to less durable material may lead to microbial colonisation and biofilm formation. The formation of a fibrin sheath within and around a catheter and within the vessel wall can create a nidus for thrombus formation that promotes the generation of a biofilm which traps bacteria. Adaptive resistance to organisms by preventing adequate antimicrobial penetration through the fibrin-polysaccharide matrix layers finally leads to persistent bacteraemia and potential downstream complications (septic shock, metastatic infections, etc.)[16,17].

Several risk factors have been proposed for the development of CRBSI. These can be either catheter-related (catheter type, insertion site, duration of catheter use) or patient-related (younger age, immunodeficient state, prior bacteraemia or CRBSI of the current catheter, high ferritin, low albumin level, long-term IV iron use, nasal carriage of *Staphylococcus aureus* [*S. aureus*])[16,18,19]. The only risk factor for CRBSI in the IPHN report was younger age. On the other hand, access site, number of cuffs, the frequency of exit-site care, catheter lock solution type, and type of disinfectant used at the catheter ES had no impact on the infection rate according to the large-cohort IPHN data[6].

PREVENTION OF HAEMODIALYSIS CRBSI

Educating patients and HD staff about both the risks of long-term catheter use, and optimal catheter care are key components for reducing CRBSI. Established protocols for sterile insertion techniques, including hand hygiene with maximal barrier precautions and strict adherence to universal asepsis rules while handling catheters are essential. Attention to proper catheter exit-site care, hub disinfection using recommended antiseptic agents, and the use of recommended topical ointments during exit-site dressing changes are important core interventions[20] (Table I). Before application of any product to the catheter, it is important to first check with the manufacturer to ensure that the selected ointment will not interact with the catheter material.

There is no observed benefit in the administration of antibiotics before the insertion of long-term CVCs to prevent gram-positive CRBSI[5,21,22]. On the other hand, infection rates decreased over years with the appropriate preventive and therapeutic interventions[18]. Recently, data from the Standardising Care to Improve Outcomes in Paediatric End-stage Kidney Disease (SCOPE) Collaborative showed a reduction in CRBSI rates from 3.3 to 0.8/100 HD catheter days with the implementation of standardised HD catheter care bundles in children[23]. Another report assessed 1277 patients with chronic HD from 35 of the paediatric dialysis centres participating in the SCOPE Collaborative. Consistent improvement in compliance with standardised HD catheter care practices in 11 centres resulted in a significant reduction in CRBSI rates over time (2.71 to 0.71/100 pt months, RR 0.98, p<0.001)[24].

Centres for disease control recommend >0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine for hands, exit-site, and hub antisepsis[21]. Paediatric studies over 20,000 HD catheter days[25] showed >0.5% chlorhexidine gluconate with alcohol to be superior to povidone-iodine for CVC exit-site care in terms of exit-site infections[25]. Transparent semipermeable dressing with sterile gauze or chlorhexidine-impregnated patches can be used. Recent practice is a chlorhexidine-impregnated patch dressing changed weekly[20]. It has been shown that the combination of chlorhexidine gluconate 2% + Isopropyl alcohol 70% for hand and skin antisepsis plus chlorhexidine-impregnated patch dressing in children results in a significant decrease in CRBSI from 2.2 to 1/1000 catheter days[25]. The application of antimicrobial ointments during dressing changes is recommended. Because of emerging mupirocin resistance and its limited bacterial coverage, triple antibiotic ointment – bacitracin/gramicidin/polymyxin B, bacitracin/gramicidin/neomycin ointment, or povidone iodine ointment at the CVC exit site is recommended for preventing exit-site infection and CRBSI[21]. A SCOPE Collaborative study determined the risk factors associated with increased CRBSI rates to be mupirocin use at ES or no antibiotic use at ES[24].

Preventing catheter hub contamination with chlorhexidine gluconate-based rather than alcohol-based surgical scrubs is also suggested. Novel therapies, including hub devices containing chlorhexidine may further reduce bloodstream infections in selected catheter-dependent HD patients at increased risk for recurrent CRBSI at facilities with uncontrolled rates of infection[3,9,16,20,21,26]. The KDOQI considers it reasonable to use an antimicrobial barrier cap to help reduce CRBSI in high-risk patients or facilities; the choice of connector should be based on the clinician's discretion and best clinical judgment (i.e., Tego needle-free HD connector)[3]. Chlorhexidine-embedded rod devices (i.e., ClearGuard), which extend from the inside of the cap to the catheter lumen, are novel options for CRBSI prevention. The cap is used in place of a standard cap or connector. When this cap is inserted into a liquid-filled catheter, chlorhexidine slowly elutes from the rod into the catheter lock solution to eliminate contaminating microbes near the hub and in that portion of the catheter limb. Use of these caps for 13 months was associated with a 63% lower CRBSI rate *vs*. the use of Tego caps[27].

CATHETER-RELATED BLOODSTREAM INFECTION (CRBSI)

There should be a high suspicion of CRBSI when a patient on HD develops fever or chills during the session and there is no evidence of a source of infection at another body site after the appropriate clinical and laboratory evaluation. Signs of sepsis (hypotension, tachycardia, altered mental status, etc) and flow problems (clot, fibrin sheath, prior asymptomatic biofilm seeding) may be seen. There may also be concomitant exit-site/tunnel infections characterised by erythema at the exit site, and purulent discharge, induration, and tenderness at the subcutaneous tunnel may be indicative[16].

Table I. Topical antimicrobial ointments and dressings used for the prevention of infection in haemodialysis catheters (adapted from reference 20).

CATHETER EXIT-SITE DRESSINGS	CATHETER EXIT-SITE OINTMENTS	INTRANASAL OINTMENTS
Chlorhexidine-based skin antiseptic	Triple antibiotic	Mupirocin
Chlorhexidine-impregnated sponge	Mupirocin	
Transparent semipermeable dressing or gauze dressing	Gentamicin	
Chlorhexidine-impregnated patch dressing	Povidone-iodine	
	Medicinal honey	
Chlorhexidine gluconate-based rather than alcohol-based surgical scrubs for catheter hubs		
Chlorhexidine-containing hub devices		
Visualisation of ES with each session, minimum weekly dressing change		

Different series found an overall infection rate with permanent CVCs of 0.26-5.7 episodes/1000 catheter days[16,18,23] and the IPHN registry reported 1 per 26 catheter-months (1.3/1,000 catheter-days)[6]. Systemic infection occurred in 53 cases (including 33 septic episodes), whereas local infections of the CVC exit-site, tunnel, or CVC itself occurred in 20 cases[6].

DIAGNOSIS OF CRBSI

Differential time to positivity is critical to detect CRBSI. Two blood cultures determine this: a blood culture from CVC that is at least 3 times higher in the number of bacterial colonies than a peripheral culture or a blood culture from the CVC lumen with a growth of microorganisms at least 2 hours earlier than cultures from a peripheral vein. Even though isolation of the same organisms from the CVC lumen and peripheral vein is critical for diagnosis, HD-patient vein preservation is of particular importance and thus the IDSA agreed to accept CVC and HD bloodline (circuit) connected to CVC, in accordance with ERBP recommendations[5,28]. When blood culture methods are insufficient to detect causative agents, more sophisticated non-culture-based laboratory techniques including genetic and spectroscopic (RT-PCR or PNA-FISH or MALDI-TOF) tests may be helpful in certain cases[29].

CAUSATIVE AGENTS FOR CRBSI

According to IPHN data, the cause of CRBSI was gram-positive bacteria in 63% of episodes, and 17% of blood or exit-site cultures were negative[6]. The national Canadian dataset showed coagulase-negative *Staphylococci* and *S. aureus* in 40% and 32% of the episodes, respectively, and 10% of the episodes emerged from gram-negative bacteria[30]. A paediatric study from Sri Lanka showed that coagulase-negative *Staphylococci* were significantly associated with right-sided infective endocarditis following asymptomatic CRBSI episodes. Therefore, appropriate investigations are of pivotal importance in all CRBSI episodes[31].

TREATMENT OF CRBSI

Figures I and II summarise CRBSI management. The empiric therapy of CRBSI is usually a combination of a glycopeptide antibiotic (vancomycin or teicoplanin) for a possible MRSA infection and a broad-spectrum cephalosporin or an aminoglycoside in the case of gram-negative bacteria. The initial empiric antibiotic treatment should be guided by local resistance patterns. When sensitivities of the pathogen become available, the empiric treatment should be appropriately modified. If possible, aminoglycosides should be avoided. If unavoidable, it is important to administer them 1 hour before the dialysis session and deliver highly efficient dialysis afterwards. If methicillin-sensitive *S. aureus* (MSSA) is cultured, the advice is to switch to cefazolin[5,16,18]. All antimicrobial doses should be based on paediatric dosing recommendations for HD patients and on safe blood levels to re-dose, where available and applicable (i. e. for vancomycin and aminoglycosides[16]. Vancomycin should be used judiciously and correctly in the

Figure I. Management of catheter related bloodstream infections in HD (adapted from references 5,16) patients.

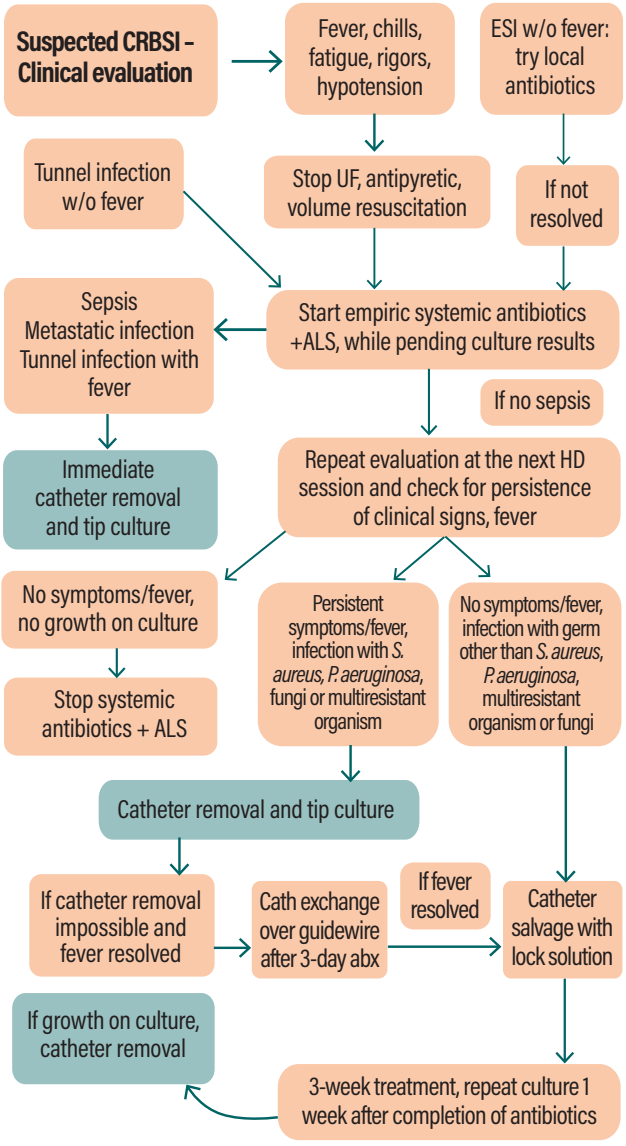
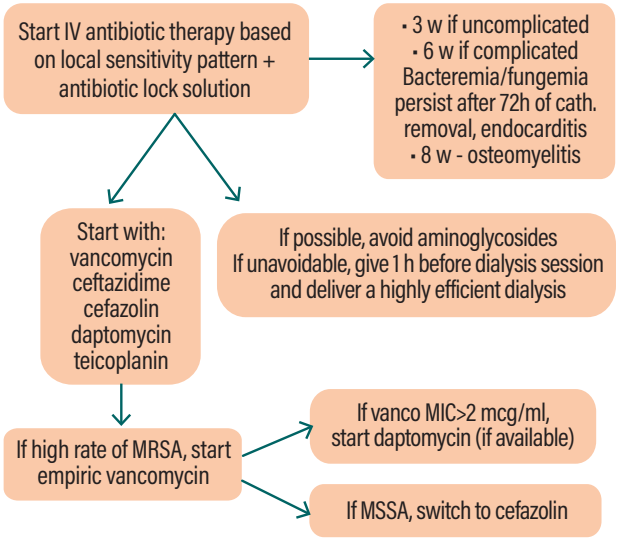


Figure II. Antibiotic treatment in catheter related bloodstream infections in HD patients (adapted from reference 5).



ESKD population, where its empiric use is warranted but where culture-sensitivity data requires timely follow-up to facilitate a switch to alternative antibiotics where sensitivity results indicate they would be more appropriate. Vancomycin is inferior to other parenteral anti-staphylococcal agents such as cefazolin and cloxacillin in MSSA CRBSI cases[28]. Patients infected with MSSA were often kept on treatment with vancomycin rather than switched to cefazolin, despite culture results, which resulted in more treatment failure, more hospitalisation, and higher mortality. As vancomycin is a cell wall inhibitor, not bactericidal, and it has no bolus dose, higher minimal inhibitory concentrations (MIC) are necessary with vancomycin in heterogeneous vancomycin-intermediate *S. aureus* (hVISA) isolates, and there may also be vancomycin-resistant *S. aureus* isolates. If vancomycin MIC>2 mcg/ml or if the patient is allergic to vancomycin, daptomycin can be started[5].

Antimicrobial treatment should be continued for 3 weeks with appropriate coverage. In endocarditis and in metastatic infection like septic arthritis, antibiotherapy should continue up to 6-8 weeks after catheter removal (Figures I, II)[5].

Indications for catheter removal include severe sepsis/septic shock, metastatic infection, infection with *S. aureus*, *P. aeruginosa*, fungi or multiresistant organisms, persistently positive blood cultures, and tunnel infection[2,18,19,30,31]. It is also possible to use systemic antibiotics and perform interventional procedures like catheter replacement via guidewire exchange or simultaneous removal and insertion of a new catheter, but this involves potential adverse effects that include vein damage and bleeding (Figure I)[16,17,32,33].

Systemic antibiotics alone result in a success rate of ~30–45% (high relapse rate). The current recommendation for treatment of CRBSI is systemic antibiotics + an antibacterial lock as early as possible (+ anticoagulant)[17,33,34]. A retrospective study evaluating 95 CRBSI episodes in 43 children showed that HD catheters in the high-risk group (defined as those with septic episodes or >10 CRBSI episodes) who were receiving ABL (Tobra 5 mg/ml + rt-PA) prophylaxis had statistically longer overall survival times than those in the high-risk group not receiving ABL prophylaxis35. If aminoglycosides are used, higher concentrations (i.e., 2.7 mg/mL gentamicin) should be avoided. A low-dose gentamicin–citrate lock (0.32 mg/ml of gentamicin in 4% citrate) versus a standard heparin lock (1000 U/ml) showed a significant reduction in CRBSI and a significant reduction in gentamicin resistance among adult HD patients[36].

ANTIMICROBIAL LOCK SOLUTIONS

Antimicrobial lock solutions (ALS) are defined as a high concentration of antibiotics within the catheter lumen throughout the entire interdialytic period to increase the chances of eradicating any pathogens within the biofilm. It is estimated that antibiotic concentrations from 10 to 100 times the MIC can be achieved in an antibiotic lock, far exceeding the ongoing antibiotic concentration achieved by the infusion of systemic antibiotics alone[37]. These agents can be based on antibacterials (i.e., vancomycin, gentamicin, tobramycin, cefazolin, ceftazidime), antimicrobials (i.e., taurolidine), or anticoagulants (i.e., heparin, citrate, urokinase, recombinant tissue plasminogen activator [rt-PA]), or a combination of these agents (Table II). The use of prophylactic antimicrobial lock solutions with or without the addition of an anticoagulant has been suggested as a method for the prevention of CRBSI by impeding biofilm formation, killing bacteria, and/or inhibiting bacterial growth in selected individuals. Double or triple combinations as well as 2+1 protocols are being used in some trials and in practice[20] (Table II):

Different concentrations of heparin (most commonly 5000 U/mL) have been widely used as an ALS. The optimal concentration, which ranges from 1000 to 10,000 U/mL has not been clearly defined. The use of 5000 U/mL and higher concentrations is associated with an increased risk of bleeding complications because of spilling into the circulation. Different studies show that antibiotics, citrate, or rt-PA as an ALS have significant benefits over heparin in reducing CRBSI[30]. At present, 4% citrate solution seems to offer the best benefit/risk ratio compared to higher concentrations. Biofilm-removing properties and intrinsic antimicrobial activity is preserved with the lower citrate dose. Higher doses involve a risk of hypocalcaemia and arrhythmia. A meta-analysis evaluating lock solutions with standard heparin *versus* low to moderate concentrations of citrate demonstrated the superiority of antibiotic-citrate over heparin in decreasing both CRBSI and risk of bleeding[38]. Alternative ALS including a combination of heparin with citrate and taurolidine showed a significant reduction in staphylococcal infections[43]. Additionally, another meta-analysis demonstrated the effectiveness of taurolidine in reducing gram-negative infections[44]. Bicarbonate lock *vs.* saline, and bicarbonate *vs.* heparin studies found conflicting results[40,41]. Table III summarises the results of other meta-analyses and systematic reviews in adults.

Recent studies suggest the advantage of 2+1 protocols, i.e., taurolidine-based solutions with the addition of urokinase once weekly, or rt-PA instead of heparin once weekly, as compared with heparin 3 times a week, which seem to significantly reduce the incidence of catheter malfunction and bacteraemia[39,42]. Specifically, the use of taurolidine-based catheter lock solutions containing heparin and urokinase significantly reduced complications related to tunnelled HD catheters when compared to 4% citrate solution, and were overall more cost-efficient[39]. Additionally, the use of rt-PA instead of heparin once weekly, as compared with heparin 3 times a week, significantly reduced the incidence of catheter malfunction and bacteraemia[42]. However, this issue needs to be confirmed by further research.

Antibiotic-containing catheter lock solutions are not routinely recommended in the prevention of CRBSI due to the risk of the emergence of resistant organisms, despite having shown a relatively smaller risk than previously believed[17,46]. These solutions should be reserved for patients at increased risk for recurrent CRBSI or in facilities with uncontrolled rates of infection[3,5,16,21,45]. Additionally, the risks (arrhythmias, toxicity, allergic reactions, development of resistance to antibiotics) should be weighed against the benefits in terms of preventing infection[5,21,38,45].

Table II. Nonantibiotic lock solutions[5,21,36,38].

GROUP NAME	ACTION	COMMENT
Heparin (1000-10,000 U)	Anticoagulant.	Optimal concentration? >5000 U/mL - Risk of bleeding risk. - Thrombocytopenia. - Promotes biofilm production. - CNS species resistant after use of heparin-gentamicin lock.
Trisodium Citrate (4% to 46.7%)	Prevents biofilm formation, causes less bleeding. Citrate 4% has the best cost-effectiveness and safety profile. Citrate 4% in combination with other locking agents – effective (see below).	30% - 46.7% - Not FDA approved, withdrawn. Excessive overfill may result in death, paraesthesia, cardiac and embolic complications due to the precipitation of trisodium citrate in CVC. Citrate 4% alone – not effective.
Taurolidine 1.35%	Antiseptic properties, with activity against both gram-positive and negative species. Reduces biofilm formation and has a low-risk bacterial resistance.	
Urokinase* 25,000 U	Antifibrinolytic.	
rt-PA 1 mg/mL	Antifibrinolytic.	The use of rt-PA instead of heparin once weekly, compared to heparin 3 times a week, significantly reduced both the incidence of catheter malfunction and bacteraemia[39].
Methylene blue and its combinations	Chelator-based lock solution.	No FDA approval. Limited experience.
Bicarbonate 8.4% and 7.5%)		More effective than normal saline for preventing catheter loss due to catheter thrombosis and CRBSI[40], but less effective than heparin in terms of catheter loss due to thrombosis[41].
DOUBLE – TRIPLE COMBINATIONS • Antibiotic/heparin is more effective than heparin. • Antibiotic/citrate is more effective than heparin. • Taurolidine/citrate is more effective than heparin. • Taurolidine/citrate/heparin 500 U is more effective than heparin 5000 U.		
2 + 1 PROTOCOLS • Taurolidine/citrate/urokinase, 25,000 U once a week + taurolidine/citrate/heparin 500 U twice a week is more effective than sodium citrate 4% alone in terms of catheter patency, reducing CRBSI and hospitalisation[42]. • rt-PA once a week + heparin 5000 U twice a week is more effective than heparin 5000 U 3 times a week.		

*Not widely available, rt-PA: Recombinant tissue plasminogen activator.

Table III. Meta-analyses and systematic reviews on antimicrobial lock solutions in HD patients.

Labriola L, *et al.*[47]	Meta-analysis RCT and observational studies 1999-2007	Tunnelled and ununnelled. Acute and chronic HD. Heparin 5000 U/mL *vs.* ALS (gentamicin-citrate, gentamicin-heparin, taurolidine-citrate, minocycline-EDTA, citrate 30%, cefotaxime-heparin, cefazolin-gentamicin-heparin).	Use of an ALS decreases the risk of CRBSI by approximately a factor of 3.
Jaffer Y, *et al.*[48]	Meta-analysis	Tunnelled and ununnelled. Acute and chronic HD. Heparin 5000 or 1000 U/mL *vs.* ALS (gentamycin, cefotaxime, minocycline, cefazolin, taurolidine-citrate, 30% citrate).	CRBSI was 7.72 times less likely when using ALS. Rates of catheter thrombosis did not increase.
Grudzinski A, *et al.*[49]	Meta-analysis/ Systematic review	Tunnelled and ununnelled. Acute and chronic HD. Citrate-only locking solutions *vs.* heparin.	Bacteraemia tended to be lower with citrate but not statistically significant. Significantly lower risk of bleeding in the citrate group. No difference in patency or hospitalisation.
Wang Y, *et al.*[45]	Cochrane review	Tunnelled and ununnelled. Chronic HD. Heparin 5000 U/mL, low dose or no heparin, citrates, antibiotic locking solutions, rt-PA, ethanol).	Significant reduction in CRBSI for citrate, antibiotics, rt-PA, but not for ethanol or low dose heparin and systemic agents. Additional use of antibiotic locks to citrate has no additional impact on CRBSI.
Zhao Y, *et al.*[38]	Meta-analysis (RCT)/ Systematic review	Tunnelled and ununnelled. Acute and chronic HD. Citrate *vs.* heparin; citrate+other antimicrobial solution *vs.* heparin.	Citrate lock concentrations of 1–7% associated with decreased in CRBSI, high concentrations (30–46.7%) had no effect. - Addition of an antimicrobial substance to citrate was associated with decrease in CRBSI. - Risk of bleeding was lower for citrate than heparin.
Sheng KX, *et al.*[50]	Meta-analysis/ Systematic review	Heparin 5000 U/mL; low-dose heparin, antibiotics (cloxacillin, cefotaxime, linezolid, vancomycin, gentamicin) combined with anticoagulants (e.g., heparin, citrate, EDTA, urokinase), minocycline, taurolidine, ethanol.	Ethanol+antibiotics+anticoagulant *vs.* heparin were more effective in preventing CRBSI. Low-dose heparin and citrate had lower bleeding risk than heparin. Using gentamicin was connected to bacterial resistance after 6 months and to ototoxicity.

In conclusion, CVC remains the most commonly used VA in children due to its advantages of simplicity of placement, immediate use, and needle-free connection. CRBSI remains a major concern in many HD units for children. To decrease CRBSI, universal precautions, a sterile environment, and an aseptic technique should be applied on any occasion when a venous catheter is manipulated, connected, or disconnected. Anti-microbial lock solutions should never replace hygienic standards, universal precautions and good clinical practice statements with regard to catheter care and handling. Appropriate management of CRBSI with systemic antibiotics based on culture sensitivity results and antibiotic locks is essential. Routine prophylaxis with ALS is not recommended unless an increased risk of CRBSI exists.

KEY TAKE-HOME MESSAGES - ANTIMICROBIAL LOCK SOLUTIONS

- Antibiotic lock solutions are indicated during the treatment of uncomplicated CRBSI in conjunction with systemic antibiotics as early as possible (within the first 48–72 hours of the diagnosis of a CRBSI) and for prevention of CRBSI in children with an increased risk of developing an infection.
- Routine prophylactic ALS is not recommended.
- ALS-associated risks (arrhythmias, toxicity, allergic reactions, development of resistance to antibiotics) should always be weighed against the benefits in terms of prevention of CRBSI.
- ALS should never replace hygienic standards and universal precautions with regard to catheter care and handling.

KEY TAKE-HOME MESSAGES – MANAGEMENT OF CRBSI

- Blood cultures should be obtained from the catheter hubs/HD circuit prior to antibiotic treatment.
- Broad-spectrum antibiotics such as vancomycin and ceftazidime are commonly used empirically while awaiting culture results.
- CRBSI should not be treated with systemic antibiotics alone, and an antibiotic lock should always be added at least 2–3 weeks after negative blood cultures are first obtained; complicated infections may require longer therapy.

KEY TAKE-HOME MESSAGES – CATHETER REMOVAL

- CRBSI with pseudomonas, *Staphylococcus aureus*, or fungi generally mandates catheter removal.
- Persistently positive blood cultures or recurrent symptoms during antibiotic treatment also require HD catheter removal; wire-guided exchange can be safely used for most patients.

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