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Prevention of Catheter-related Bloodstream Infection in Patients on Hemodialysis CME

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Abstract and Introduction

Abstract

Central venous catheters (CVCs) are frequently used as vascular access for patients who require hemodialysis, but infectious complications remain a major clinical problem. Specifically, catheter-related bloodstream infections (CRBSIs) have an adverse effect on survival, hospitalization, mortality, and the overall cost of care in this setting. The growing number of patients who require hemodialysis, combined with an increasing number of patients who cannot use any vascular access other than a CVC, stress the importance of strategies to prevent CRBSI. Various interventions aimed at reducing the incidence of CRBSI are available, but they have not yet been integrated into evidence-based, consensus guidelines. In this Review, the results from several CVC infection prevention studies—of patients from dialysis and nondialysis settings—are combined to outline a rational approach to CRBSI prevention. Prevention of intraluminal contamination of the CVC is pivotal and of proven efficacy, as are strict aseptic CVC insertion and handling protocols, use of chlorhexidine in alcohol solutions for skin cleansing, topical application of antimicrobial ointments, and antimicrobial lock solutions. Adherence to a meticulous catheter care protocol can achieve a CRBSI incidence well below one episode per 1,000 catheter days, even without the need for antimicrobial ointments or lock solutions.

Introduction

The use of central venous catheters (CVCs) contributes substantially to infectious complications in patients treated by hemodialysis, although CVCs are only used in a minority of these individuals.[1] In addition, infection is the principal reason for CVC removal, and CVC-associated bloodstream infections are associated with substantial health-care costs and increased mortality.[2-4] Guidelines, such as the European Renal Best Practice (ERBP) position statement and those from the Kidney Disease Outcomes Quality Initiative (KDOQI), stress the importance of reducing the use of CVCs. However, in most dialysis clinics, at least 10-20% of patients have a CVC.[5] As the population of patients who require hemodialysis is growing, an increasing number of patients require a CVC because other options for vascular access, such as an arterio-venous fistula or graft, have failed or are not possible.

The number of well-designed, randomized, controlled trials (RCTs) specifically looking at prevention of infection in patients with CVCs used for hemodialysis is small. However, many studies have examined the efficacy of antimicrobial lock solutions and ointments applied to the catheter exit site in hospitalized patients who are not on dialysis. In addition, a consistent, standardized approach to the definitions of exit-site infections and CVC-associated bloodstream infections has not been followed in published studies, which hampers the comparison of data.

This Review aims to outline a rational strategy for reducing the incidence of CVC-related infections in patients on hemodialysis. Such infections can be divided into exit-site infections and bloodstream infections. The latter will be discussed in the most detail and, in line with current literature, will be referred to as catheter-related bloodstream infections (CRBSIs). The information presented in this article represents the opinion of the author and accordingly, where noted in the text, the conclusions reached occasionally differ from those in current guidelines.

Pathogenesis of CRBSI

Understanding the sequence of events that leads from catheter insertion to CRBSI is essential for development of a rational approach to CRBSI prevention. In addition, the incidence of CRBSI shows remarkable variation between different dialysis centers, both in Europe and the USA. At least a 10-fold difference in CRBSI incidence has been reported, ranging from 0.5 to 6.6 episodes per 1,000 catheter days.[6,7] The mechanisms underlying these large differences need to be recognized and understood. Some of the variability could be related to differences in definitions of CRBSI, but most probably represents heterogeneity in the clinical management of patients and in adherence to catheter care guidelines.

The Role of Bacterial Biofilms

CRBSI arises from bacterial seeding from biofilms that form on either the inside or outside of indwelling catheters. A biofilm is a structural community of bacteria enclosed in a self-produced matrix, with or without host constituents, that is firmly attached to the catheter surface. This matrix allows the sessile bacteria to survive in a hostile environment and grow in a very slow fashion. The susceptibility of bacteria in a biofilm to antimicrobial agents is dramatically decreased, by at least 10-100-fold. Adherence of contaminating bacteria to the CVC is a prerequisite for biofilm formation to take place. In the first 2 weeks after catheter placement, formation of a biofilm on the outside of the CVC and subsequent surface migration of bacteria into the bloodstream is importance for CRBSI to occur. Thereafter, bacterial contamination of the catheter hub is the most frequent route of bacterial spread to the internal catheter surface. After several weeks *in situ,* virtually all CVCs have an intraluminal biofilm.[8] However, it is clear that not all of these patients will inevitably develop CRBSI and CVCs may be in place for many years without causing CRBSI. What factors cause or allow the seeding of bacteria from the CVC biofilm into the bloodstream is not known, but most likely will at least partly depend on the species and strain of the bacteria within the biofilm.

Genotyping of *Staphylococcus epidermidis* isolated from device biofilm, blood, catheter hub and exit-site skin of patients with CVCs has revealed that most (if not all) bacteria grown from the CVC lumen and blood are similar to those grown from the CVC hub, and that the same types are also frequently found on the exit-site skin.[9] This finding has important implications, as it gives experimental support to the notion that control of bacterial biofilm formation on the hub and exit-site skin is a very important element for prevention of CRBSI. The importance of catheter exit-site care in the presence of an already established biofilm on the inside of the CVC lumen seems contradictory. However, exit-site care may prevent colonization with bacteria such as *Staphylococcus aureus* that carry a high risk for CRBSI after intraluminal contamination. It is even hypothetically possible, that a pre-existent intraluminal biofilm made up of bacteria with low virulence (that is, at low risk for seeding into the bloodstream) actually reduces the risk for subsequent colonization with more virulent bacteria.[10]

Quorum Sensing

For biofilm formation to occur, bacterial quorum sensing (QS) systems need to be activated. QS systems are microbiological pathways that have been discovered over the past decade. They are involved in the detection of extracellular small molecules that initiate signaling cascades and in the alteration of gene expression in response to bacterial population density.[11] Essentially, they control bacterial behavior once a critical population density is reached. QS systems are not only important for biofilm formation,[11] but also control a wide range of genes— for instance, those that express virulence factors and antibiotic resistance.[12] These new insights have led to a novel area of microbiology, so-called sociomicrobiology. This field is based on the understanding that bacterial decision-making is not done by individual bacteria, but is a collective process based upon the sharing of information and collaboration. From a clinical perspective, this knowledge underlines the importance of controlling bacterial contamination of the CVC. Contamination with a low bacterial cell density will not lead to induction of QS systems: keeping bacterial populations small will, therefore, hamper biofilm formation and subsequent permanent colonization of the catheter surface. In addition, characterization of the signaling molecules and pathways that are involved in QS has led to the development of a number of new therapeutic targets and strategies. For example, natural and synthetic molecular mimics of the QS signaling pathway elements and protective antibodies generated by vaccination against these molecules are under study as potential inhibitors of QS.[13]

Essential Elements of Catheter Care

A CRBSI incidence below one episode per 1,000 catheter days is possible using standard antiseptic precautions, and could be used as a benchmark by which to assess the quality of catheter care.[14,15] Having adequately trained staff who adhere to the CVC care protocol is, however, an essential element to reach this low rate of infection.

In several studies, the introduction of a meticulous catheter care protocol has resulted in a very substantial reduction in the incidence of CRBSI. However, no prospective RCTs have been conducted on this topic and in general the efficacy of a catheter care protocol is measured by comparison with a historic rate of infection. Most studies have been conducted in intensive care units;[14,16,17] however, one study involved a group of stable patients on hemodialysis.[18] In this study, introduction of a catheter care protocol that followed the guidelines published in 2002 from the Centers for Disease Control and Prevention (CDC) resulted in a decrease in CRBSI incidence from 6.7 to 1.6 episodes per 1,000 catheter days.[18] Introduction of the catheter care protocol involved strict adherence to guidelines for use of aseptic conditions during CVC placement, exit-site care, and in the connection and disconnection of blood lines. The researchers concluded that the introduction of and adherence to a strict aseptic catheter care protocol may lead to a substantial and sustained reduction in the incidence of CRBSI.[19] However, despite the large body of evidence in support of simple but effective protocols to reduce the incidence of CRBSI, widespread use in the healthcare community has been challenging as it requires continuous training and education of the medical and nursing staff.[20-22]

Meticulous catheter care is instrumental in ensuring a low CRBSI rate and should cover the surgical procedure of catheter placement, exit-site care, connection and disconnection of blood lines, and the replacement of malfunctioning catheters over a guidewire (Table 1). Some of the elements discussed in this section are of proven value, as their effect on reduction of CRBSI incidence has been confirmed by RCTs. Others are based on common sense and/or by inference from the results of other studies not directly related to CRBSI.

Table 1. Outline of a Central Venous Catheter Care Protocol

Type of handling	Preventive measures	Optional extra measures*
Catheter insertion	Avoid femoral vein insertion sites Introduce maximal sterile barrier precautions: wash hands with antiseptic soap or solution; wear a surgical mask, sterile gloves, cap, and use sterile instruments; use a sterile sheet to cover the patient; disinfect skin at insertion site with povidone–iodine or 2% chlorhexidine in alcohol solution	Eradicate *S. aureus* nasal carriage by topical mupirocin for 2 weeks, followed by a once-weekly maintenance dose of the same agent
Inspection of exit site	Visual inspection and palpation with sterile or clean gloves at every dialysis session Look for signs of infection, such as swelling, pain, redness and pus Swab and culture when infection is suspected When clinical suspicion of infection is high start prophylactic antibiotics that are effective against *S. aureus*	Have a low threshold for removing nontunneled central venous catheters (author's personal opinion)
Change dressings	Change dressings at every dialysis and promptly replace loosened or soiled dressings Before applying a new dressing, clean skin with antiseptic solution, preferably a 2% chlorhexidine in alcohol solution Use nonocclusive or semipermeable dressings Note that a fully ingrown, cuffed, tunneled central venous catheters may not need a dressing	Application of a topical antimicrobial agent to the exit site, such as medicinal honey, mupirocin, or antibiotic-containing ointments
Opening and closing the central venous catheter	Wash hands with an antiseptic soap or sterile solution Wear sterile gloves, surgical mask, sterile gown Place a sterile sheet under the central venous catheter Soak the catheter hub in an antiseptic solution (such as 2% chlorhexidine in alcohol) for at least 5 min Minimize exposure of the opened catheter hub to air	Lock the central venous catheter using an antimicrobial solution A membrane-closed or needleless connector device may be used, but the effect on the incidence of catheter-related bloodstream infection is unknown
Catheter replacement over a guidewire	Use sterile barrier precautions similar to those applied when inserting a new central venous catheter	Intravenous vancomycin 1 g after replacement (author's personal opinion)

*Extra preventive measures should be taken when the incidence of catheter-related infection remains persistently above the benchmark rate. Adherence to the catheter care protocol and training of staff should be ascertained.

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Placement of the Central Venous Catheter

Aseptic Technique. First and foremost, placement of a CVC should be performed under maximally aseptic surgical conditions.[23,24] The skin should be cleansed with 2% chlorhexidine in alcohol solution, which is superior to iodine-based solutions for prevention of infection.[25] 4% chlorhexidine in alcohol solution is available, but has not been specifically studied in this setting. Periprocedural administration of antibiotics does not reduce the incidence of CRBSI and, therefore, should not be part of the care protocol.[6,26,27]

Catheter Material and Design. The material a CVC is made from influences the adherence of bacteria to the surface, which may affect biofilm formation and the patient's subsequent risk of CRBSI.[10] Most dialysis catheters are made of silicone or

poly-urethane; however, whether these materials differ in their susceptibility to biofilm formation after catheter placement has not been studied.

Some CVCs are designed for subcutaneous tunneling with a cuff that allows for ingrowth of fibroblasts, which secures the catheter in place. The ERBP position statement and KDOQI guideline explicitly advise the placement of a tunneled CVC for long-term use (>3 weeks), based on pathophysiological considerations and a generally lower rate of infection of tunneled, cuffed catheters compared to nontunneled, uncuffed catheters in several series of patients.[28,29] However, whether a tunneled or nontunneled CVC is used is not the only determinant of CRBSI risk. The National Kidney Foundation (NKF)-KDOQI guidelines acknowledge that there is a large variation in CRBSI incidence and note the dominant influence of the catheter care protocol. In addition, the introduction of tunneled, cuffed catheters has not led to a reduction in CRBSI-related complications (NKF-KDOQI guidelines, update 2006, Clinical Practice Guideline 7.4).

Several RCTs have compared the incidence of CRBSI in patients with tunneled, cuffed CVCs versus those with nontunneled CVCs. A meta-analysis of these studies did not show a notable difference when the CVCs were placed in the subclavian vein.[30] Only one RCT, involving patients in an intensive care unit, showed a markedly lower infection rate when tunneled rather than non-tunneled catheters were placed in the jugular vein.[31] One RCT that compared tunneled CVCs with nontunneled CVCs in a population of patients who required hemodialysis to treat uremia syndrome has been published, and reported similar infection rates in both groups.[32]

Nontunneled CVCs are either straight or have a curve at the end, which improves positioning when placed in the jugular vein just above the clavicle. Precurved CVCs are only used in the low jugular position. In two observational studies, CRBSI rates in patients with nontunneled, precurved CVCs were similar to those in individuals with tunneled, cuffed CVCs.[33,34] Use of a precurved, nontunneled CVC in the lower jugular position limits the amount of sliding of the CVC in and out of the exit site, which may contribute to the lower infection rate observed with curved rather than straight, nontunneled CVCs.[33] In a large, randomized, multicenter study from The Netherlands that compared heparin with sodium citrate lock solutions, no difference in CRBSI rates were noted between patients with long-term use of either nontunneled CVCs or tunneled, cuffed CVCs.[35]

The current evidence is, therefore, insufficient to conclude that CVCs for either temporary or long-term use must be cuffed and tunneled to prevent infection. Strict adherence to a catheter care protocol and selection of an appropriate venous access site (as discussed in the next section), in combination with a stably positioned CVC (such as use of a precurved CVC in the lower jugular position), may offer similar advantages to tunneling in terms of a reduced incidence of CRBSI. However, factors other than a decreased risk of CRBSI also favor tunneled, cuffed CVCs over nontunneled CVCs, namely the comfort and quality of life of the individual patient, who has to carry such a CVC for long periods.

Catheter Location. The site selected for placement of a CVC is likely to influence the risk of infection. However, in an institution where the CRBSI incidence is low (indicating use of an adequate CVC care protocol) the site of venous access did not influence infection rate.[36] The negative result of this study could be attributed to inadequate statistical power to detect such an association, rather than a true effect, but the results indicate that an effective CVC care protocol is more important in preventing CRBSI than is the catheter site. A Cochrane meta-analysis of 87 studies on this issue, published in 2007, concluded that only one of the included studies met the quality criteria for randomization.[37] The results of this single study—conducted in an intensive care unit—showed that CVCs inserted in the femoral vein carried an increased risk of CRBSI.[37]

A subsequent randomized trial in a group of acutely ill patients on dialysis compared the infection rate of CVCs situated in the femoral vein with that of CVCs situated in the subclavian or jugular vein.[38] Infection rates did not differ between the groups, except in the subgroup of patients with a high BMI and a CVC in the femoral vein: this group had an increased risk of CRBSI. Furthermore, a CVC situated in the femoral vein carries an undisputed increased risk of thrombosis. Although all central veins may develop venous stenosis owing to an indwelling CVC, use of the subclavian vein for CVC placement confers the highest risk of developing this complication. CVCs should preferably be inserted in the right jugular vein, as it carries the lowest risk of thrombosis and stenosis.[37] CRBSI is associated with central vein stenosis, but a cause-and-effect relationship has not yet been established.[39,40]

Connection and Disconnection of Lines

Great care should be taken with the connection and disconnection of any lines to the CVC, and the basic recommendations for aseptic handling of the CVC should be followed.[10] A sterile barrier should be in place and the catheter hub should be soaked in and rubbed with an antimicrobial solution before opening. Hand washing and wearing of clean or sterile gloves is mandatory. The use of hair caps, masks, or sterile gowns is generally advocated, but to date these measures are of unproven value.[41] No published data have compared the efficacy of different skin cleansing protocols after CVC insertion. However, by extrapolation from the data on cleansing solutions used during catheter insertion, the use of chlorhexidine in alcohol rather than iodine seems to be a rational choice.

The CVC should be opened for the shortest time possible to minimize the risk of intraluminal infection. The frequency of opening the CVC for connecting lines can be greatly reduced by using a membrane-closed (or needleless) connector device, such as the Luer-Lock® (Becton, Dickinson & Co, New Jersey, NJ). These devices enable a secure connection with the blood line, without the need for opening the CVC. However, the efficacy of such devices in preventing CRBSI has not yet been studied in patients on hemodialysis. In other settings, such as populations of patients who require parenteral feeding, the CVC infection rate actually increased after introduction of a needleless connector device. This finding seemed to be related to a decreased adherence to antiseptic measures when connecting the feeding line to the CVC.[42-44] Even if used properly, needleless connector devices do not seem to convey protection against CRBSI.[10]

Care of the Catheter Exit Site

Exit sites should be routinely inspected for infection at every dialysis session, and subjected to swabbing and bacterial culture whenever infection is suspected. Antibiotics covering *S. aureus* should be started immediately, before the culture results are obtained, if signs of tunnel infection are present, or if local signs of infection are rapidly worsening. The existing guideline by the CDC[11] does not state an opinion about the approach to exit-site infections in different groups of patients; however, in my opinion a low threshold for starting antibiotics should be applied for patients with diabetes mellitus as this condition is a risk factor for CRBSI.[45] In patients without diabetes mellitus, the results of the bacterial culture should be used to guide the choice of antibiotic therapy.

After inspection, the skin should be cleaned with iodine—or, preferably, chlorhexidine in alcohol—as for CVC placement. Once dry, the exit site should be covered with a nonocclusive or semipermeable adhesive dressing. I prefer to use a nonocclusive adhesive dressing whenever possible, to enable maximal natural airing of the exit site. The semipermeable adhesive dressings are sometimes not water permeable enough if the skin is moist, which promotes maceration and infection of the exit site. A Cochrane systematic review from 2003 compared the efficacy of gauze and tape versus transparent polyurethane dressings for CVC exit sites, in terms of preventing catheter-related infections.[46] Six RCTs were included in the meta-analysis, but the researchers failed to show any difference between the two dressing types with respect to infection rates—primarily owing to inadequate study design.[46] One randomized trial assessed the influence of exit-site care on infection risk in patients with CVCs used for hemodialysis; however, this study also failed to show a difference in infection rate between patients using gauze or transparent dressings.[47] Chlorhexidine-impregnated dressings and sponges are available, but the evidence of their efficacy in preventing infection (as compared to appropriate skin cleansing with 2% chlorhexidine in alcohol solutions) is not convincing.[48,49] An RCT in patients on hemodialysis with CVCs did not show that these dressings conferred any additional benefit.[48,49] Well-ingrown and epithelialized exit sites of cuffed catheters can do without a dressing, although using a dressing is preferable after topical application of antimicrobial agents to keep the ointment in place. Use of topical antimicrobial agents is not considered an essential element of catheter care, but can be added to catheter care protocols to further reduce the risk of CRBSI, as discussed in more detail below.

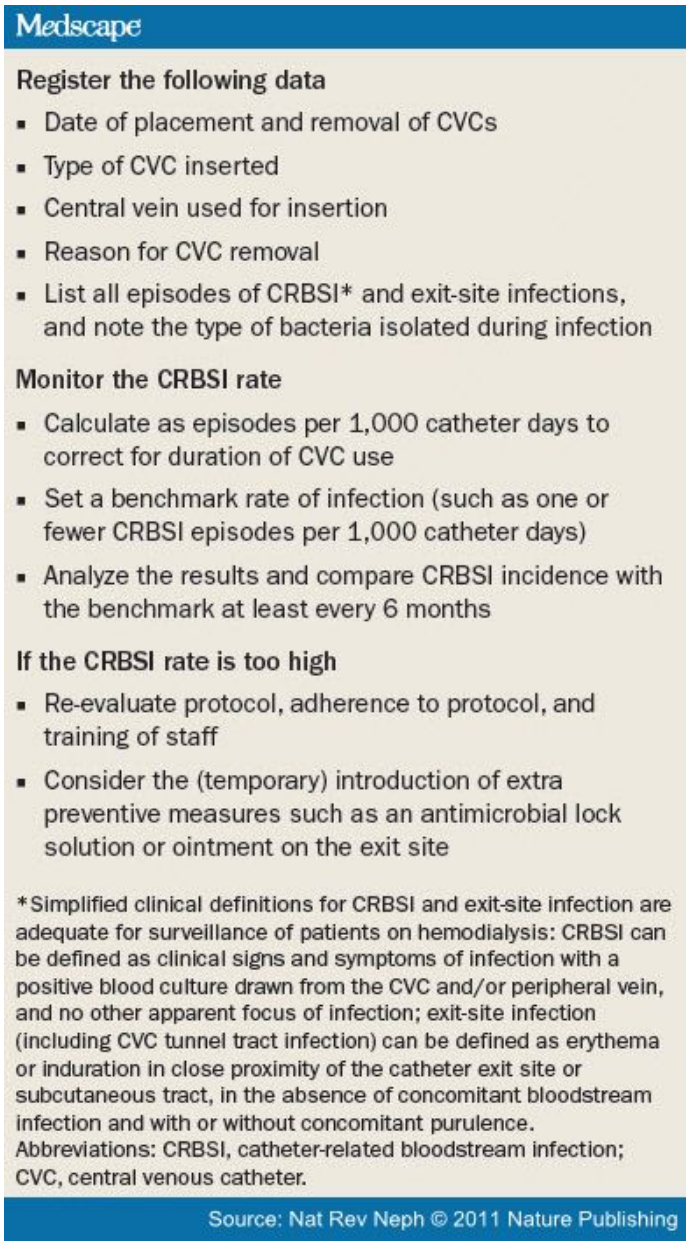
Catheter Replacement Over a Guidewire

Replacement of a CVC over a guidewire, in cases of catheter malfunction, should be done with similar antiseptic precautions as when inserting a new device. CVC replacement is associated with an increased risk of CRBSI because the exit site may be colonized with microorganisms. For this reason, I routinely administer intravenous vancomycin 1 g after a CVC exchange over a guidewire. This preventive measure is, however, not evidence-based, because studies on this subject are lacking.

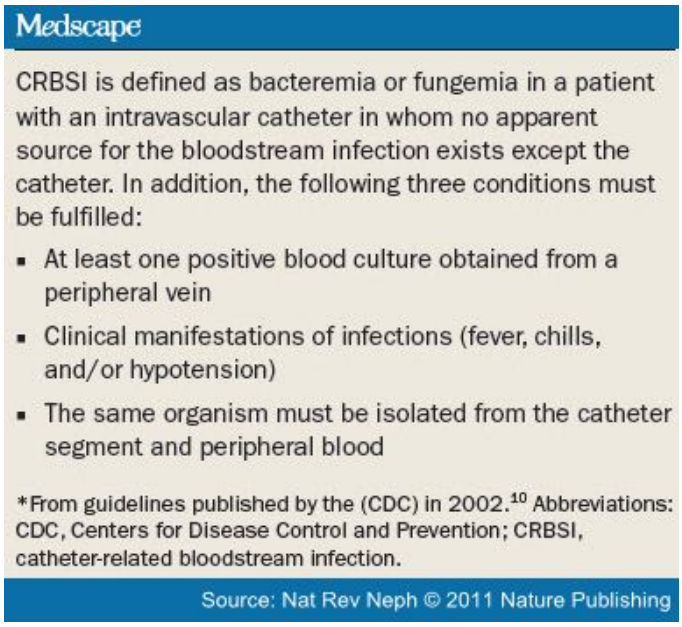
Mandatory and Complete Records

Finally, an important part of every catheter care protocol should be the careful registration of both exit site and CRBSI episodes so that an adequate response can be initiated if the dialysis center's infection rate is unacceptably high (Box 1). Adherence to internationally accepted standardized criteria for CRBSI, as defined by the CDC in 2002, is advisable (Box 2).[10] However, for stable patients on hemodialysis, inclusion in a local registry of CRBSI does not necessarily require the same organism to be isolated from the catheter segment and peripheral blood (Box 2), as the source of the bloodstream infection, catheter-related or not, is usually evident (unlike the bloodstream infections of patients in intensive care). Use of a simple and uniform clinical definition of CRBSI— clinical signs and symptoms of infection, with a positive blood culture drawn from the CVC and/or a peripheral vein, and no other apparent focus of infection—is sufficient. As most CVCs have a biofilm on the inside, a positive bacterial culture from the CVC by itself is not enough to establish a diagnosis of CRBSI.

Box 1. A Central Venous Catheter Surveillance Program



Box 2. Standardized Definition of CRBSI*



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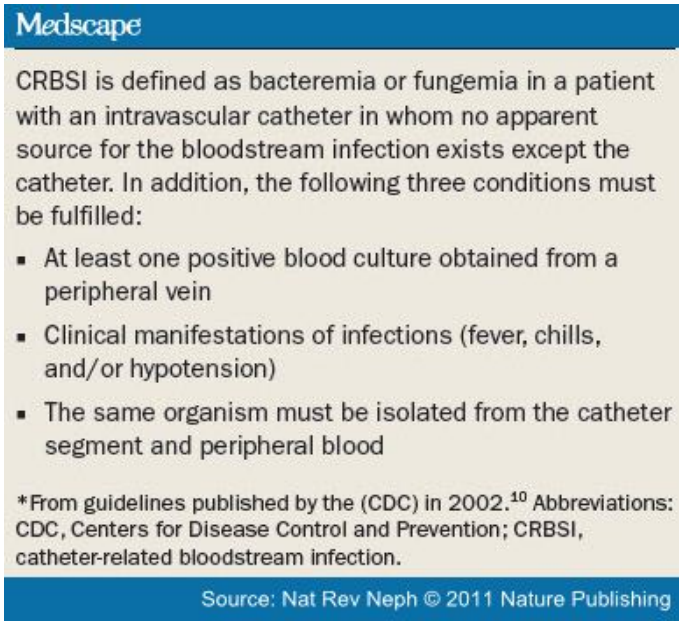


Additional Preventive Measures

Antimicrobial Lock Solutions

The efficacy of antimicrobial lock solutions to prevent CRBSI has been investigated in a number of RCTs and recently reviewed in several publications.[6,50-52] The antimicrobial lock solutions that are most studied contain either antibiotics or chemicals, such as concentrated (30% and 46.7%) trisodium citrate or taurolidine. Antimicrobial lock solutions substantially reduce the risk of CRBSI (12 trials; relative risk 0.23).[6] The currently available data do not enable a difference in efficacy to be identified between different solutions as they have not been compared in a head-to-head RCT. Of note, the follow-up of most studies was within the range 6 months to 1 year and the CRBSI rates in the control arms were, in general, well above the benchmark of one episode per 1,000 catheter days.

Potential disadvantages of antibiotic-containing antimicrobial lock solutions include induction of bacterial antibiotic resistance and aminoglycoside-related ototoxic effects. Taurolidine- and/or citrate-containing solutions do not have these disadvantages. However, antimicrobial lock solutions that contain highly concentrated trisodium citrate can briefly, but substantially, reduce the patient's concentration of plasma calcium ions, which may cause cardiac arrhythmias.[53,54] This reduction in plasma calcium may happen when the total locking volume is inadvertently pushed into the patient's blood. For this reason, approval for the use

of 46.7% trisodium citrate as an antimicrobial lock solution was withdrawn in the USA following an FDA advisory report on a fatal adverse event.[55] In addition, a case series described a possible association between pulmonary emboli and the use of a highly concentrated citrate-based lock solution.[56] Low concentrations of citrate (~4%) are advocated as a safe and cheap alternative to heparin,[57-59] but these low-citrate lock solutions display little antimicrobial activity.[60]

Other antimicrobial lock solutions have been developed based on ethanol or calcium-binding ethylenediaminetetra-acetic acid solutions, but clinical data on their antimicrobial efficacy from large RCTs are not available yet.[61-63] The ideal lock solution has anticoagulant and antimicrobial activity, is safe, does not induce bacterial resistance and can be cheaply manufactured. Lock solutions containing low concentrations of citrate in conjunction with the antimicrobial taurolidine are theoretically the best choice at this moment, but have not been widely used, nor has their efficacy been studied.[34]

Topical Antimicrobial Agents

Several published meta-analyses have studied the efficacy of disinfection of the skin and exit site in patients who have a CVC. The findings of these analyses indicate that chlorhexidine is superior to povidone-iodine for cleaning the exit site, as a 2% chlorhexidine in alcohol solution reduces the risk of CRBSI by 49%.[25] However, this conclusion is based on data from hospitalized patients with CVCs only (and five of the eight studies were conducted in intensive care units). No published data have addressed this same question in populations of patients who have CVCs used for hemodialysis.

Application of topical antimicrobial agents, such as medicinal honey,[65,66] mupirocin,[67-69] 10% povidone-iodine,[70] and bacitracin-polymyxin B[71] to the exit site may significantly reduce the incidence of CRBSI and exit-site infections in patients on hemodialysis.[6,64] A comparison between honey and mupirocin failed to show any difference in efficacy.[65] A recent Cochrane review on this subject concluded that the current data support only the topical application of mupirocin alone (among these agents) to the exit site for the prevention of CRBSI.[64] Long-term and widespread use of mupirocin may cause resistance in a high percentage (>60%) of *Staphylococcus* isolates,[72-74] but this problem has not been reported in studies of patients who have CVCs for hemodialysis. Whether topical antimicrobial treatment is of additive value in patients who already use an antimicrobial lock solution with their CVC is not known. My institution has adopted topical application of mupirocin as part of its catheter care protocol, but does not routinely check for bacterial resistance to mupirocin.

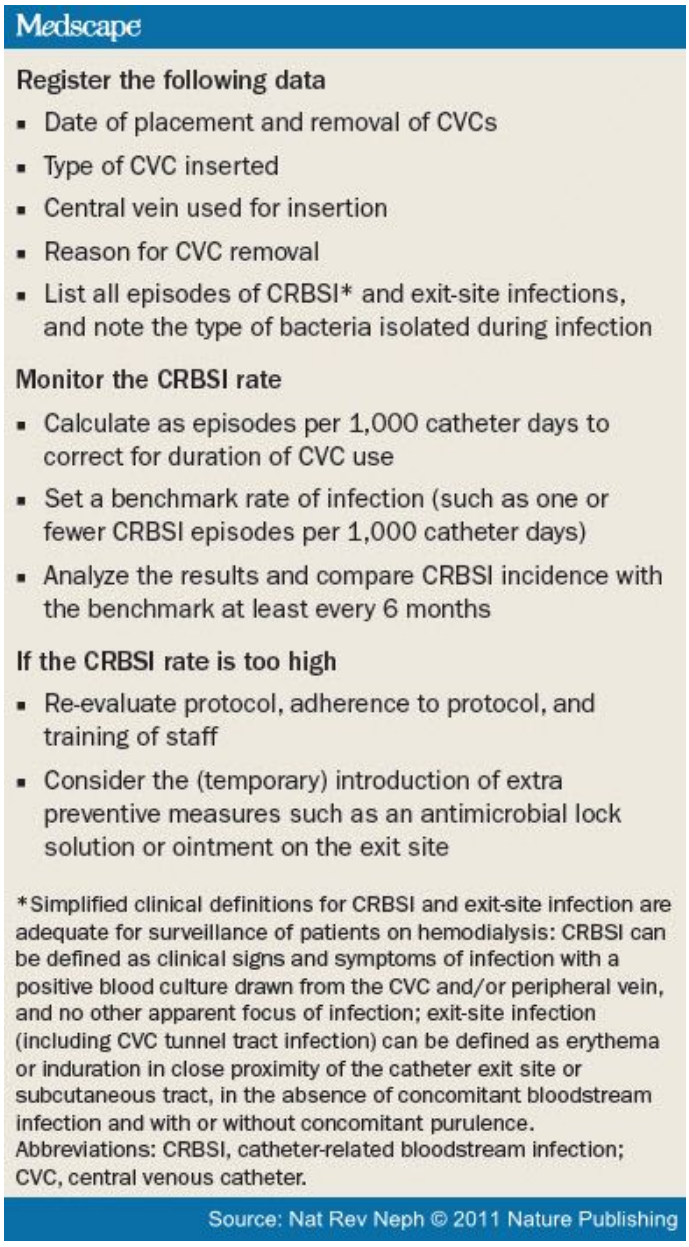
Catheters with Antimicrobial Coatings

In intensive care units, the use of catheters that are coated with antimicrobial agents or heparin is associated with a reduced catheter colonization rate and decreased CRBSI incidence.[75,76] These catheters may, therefore, be a useful option for hemodialysis in patients at an unacceptably high risk of CRBSI. Silver-coated CVCs have been studied in two RCTs involving patients on dialysis, but a statistically significant reduction in CRBSI incidence could not be demonstrated.[77,78] One RCT involving CVCs coated with minocycline and rifampicin did, however, show a significant reduction of CRBSI incidence.[79]

Eradication of *Staphylococcus aureus*

Staphylococcus species are one of the most frequent types of bacteria isolated from patients with CRBSI. Specifically, *S. aureus* is feared for its propensity to colonize prosthetic materials, heart valves, bones and joints. The mortality of *S. aureus*-related CRBSI is high and reaches an average of 20% in patients on dialysis. At least 8% of overall mortality in these patients can be attributed to *S. aureus* infection.[80] A minority of coagulase-negative *Staphylococcus* species behave as aggressively as *S. aureus* and cause potentially lethal metastatic infections.[81] Nasal carriage of *S. aureus* is common, especially among patients on dialysis, in whom it is associated with an increased risk of *S. aureus* infection.[82] Indeed, most episodes of *S. aureus* bacteremia are considered to be autoinfections.[83] Eradication of *S. aureus* nasal carriage should be attempted, because it can reduce the number of *S. aureus*-related infections in patients on dialysis, and because nasal carriage of this organism is associated with CRBSI.[84-87] Successful elimination of *S. aureus* nasal carriage can be achieved by a short (5-day) course of mupirocin applied daily to the anterior nares. After a few months, recolonization is frequent but can be reduced by once-weekly maintenance therapy or repeating the short course of mupirocin.[88] Such a strategy is effective and economical.[89] The majority of studies indicate that resistance of staphylococci to intranasally applied mupirocin is infrequently observed, but the incidence of other bacterial infections may increase.[86,88,90-96] Unfortunately, no study has yet been published that has specifically addressed the question of whether eradication of *S. aureus* nasal carriage leads to a reduced incidence of CRBSI. In my institution, every new patient who attends for dialysis (with or without a CVC) is routinely checked for *S. aureus* nasal carriage; individuals who test positive for this organism are treated with mupirocin administered to the anterior nares (see Box 1).

Box 1. A Central Venous Catheter Surveillance Program



In vitro and *in vivo* experiments have indicated that salicylic acid, a major metabolite of aspirin, has an inhibitory effect on *S. aureus* adhesion and toxin production. At daily doses of aspirin >325 mg a substantial decrease in *S. aureus*-related CRBSI was observed in patients on dialysis.[97] These data have not yet been confirmed by prospective RCTs, so routine prescription of aspirin for this reason to patients with a CVC for hemodialysis cannot yet be recommended.

Conclusions

CVCs are still frequently used as an access route for hemodialysis and are likely to remain as such over the coming years. CVC-related infections, particularly CRBSIs, are associated with high morbidity, mortality, and health-care costs. I cannot overemphasize that a stringent catheter care protocol (Table 1) is a very powerful strategy for preventing CRBSI.[98] A CRBSI rate well below one episode per 1,000 catheter days is within reach of every dialysis unit that adheres to these basic rules. Some intensive care units have shown that almost complete elimination of CRBSIs is possible.[14]

Table 1. Outline of a Central Venous Catheter Care Protocol

Type of handling	Preventive measures	Optional extra measures*
Catheter insertion	Avoid femoral vein insertion sites Introduce maximal sterile barrier precautions: wash hands with antiseptic soap or solution; wear a surgical mask, sterile gloves, cap, and use sterile instruments; use a sterile sheet to cover the patient; disinfect skin at insertion site with povidone–iodine or 2% chlorhexidine in alcohol solution	Eradicate *S. aureus* nasal carriage by topical mupirocin for 2 weeks, followed by a once-weekly maintenance dose of the same agent
Inspection of exit site	Visual inspection and palpation with sterile or clean gloves at every dialysis session Look for signs of infection, such as swelling, pain, redness and pus Swab and culture when infection is suspected When clinical suspicion of infection is high start prophylactic antibiotics that are effective against *S. aureus*	Have a low threshold for removing nontunneled central venous catheters (author's personal opinion)
Change dressings	Change dressings at every dialysis and promptly replace loosened or soiled dressings Before applying a new dressing, clean skin with antiseptic solution, preferably a 2% chlorhexidine in alcohol solution Use nonocclusive or semipermeable dressings Note that a fully ingrown, cuffed, tunneled central venous catheters may not need a dressing	Application of a topical antimicrobial agent to the exit site, such as medicinal honey, mupirocin, or antibiotic-containing ointments
Opening and closing the central venous catheter	Wash hands with an antiseptic soap or sterile solution Wear sterile gloves, surgical mask, sterile gown Place a sterile sheet under the central venous catheter Soak the catheter hub in an antiseptic solution (such as 2% chlorhexidine in alcohol) for at least 5 min Minimize exposure of the opened catheter hub to air	Lock the central venous catheter using an antimicrobial solution A membrane-closed or needleless connector device may be used, but the effect on the incidence of catheter-related bloodstream infection is unknown
Catheter replacement over a guidewire	Use sterile barrier precautions similar to those applied when inserting a new central venous catheter	Intravenous vancomycin 1 g after replacement (author's personal opinion)

*Extra preventive measures should be taken when the incidence of catheter-related infection remains persistently above the benchmark rate. Adherence to the catheter care protocol and training of staff should be ascertained.

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The stringent implementation of a standard catheter care protocol should result in a very low rate of CRBSI that obviates the need for antimicrobial lock solutions or application of an antimicrobial ointment to the exit site. However, the different antimicrobial lock solutions and topical ointments do have impressive efficacy for preventing CRBSI, and including them in routine catheter care protocols is very tempting. However, the reader should bear in mind that the risk:benefit ratio of some antimicrobial lock solutions is not clear and that their long-term prognostic implications are uncertain. The NKF-KDOQI guidelines recommend adherence to the 2002 guidelines issued by the CDC.[10] In these guidelines, antimicrobial lock solutions are not recommended for the daily routine management of patients with CVCs. However, the use of such solutions is advised in patients with recurrent episodes of CRBSI who are treated in centers already using an optimal aseptic catheter care protocol. The most recent publication from the European Renal Association advocates the use of antimicrobial lock solutions and the (temporary) use of topical mupirocin in these circumstances.[41]

In this respect, the additive value of antimicrobial lock solutions and topical ointments may be very limited.[99] In addition, they can increase the risk of unwanted side effects—such as incident hypocalcemia in the case of concentrated trisodium citrate lock solutions and induction of antibiotic resistance when, for example, gentamicin-containing lock solutions are used.[100] Antimicrobial lock solutions and topical ointments can, however, certainly help to reduce the infection rate when the incidence of CVC-related infection remains persistently above the benchmark rate. In addition, their use can be reserved for patients who have an unacceptably high risk of CRBSI or have known risk factors for CRBSIs, such as diabetes.[45,101]

In general, a high CRBSI incidence is indicative that the antiseptic catheter care protocol at a unit is deficient and maximum effort should be undertaken to revert that situation. In fact, CRBSI can be judged as a preventable complication and, as such, should be a 'non-event' in the dialysis unit. The medical and financial benefits of a very low incidence of CRBSI are readily appreciable and should be the incentive for every health-care professional working in dialysis units to apply a meticulous CVC care protocol and surveillance program.

Key Points

- Central venous catheters (CVCs) are frequently used in patients on hemodialysis, but they are associated with high morbidity, mortality and health-care costs owing to infectious complications

- Chlorhexidine in alcohol solutions for skin cleansing, topical application of antimicrobial ointments and antimicrobial lock solutions are proven to reduce the incidence of catheter-related bloodstream infections
- Strict, aseptic CVC insertion, meticulous catheter care, and implementation of a catheter surveillance program are mandatory to reduce the incidence of catheter-related bloodstream infections
- A catheter-related bloodstream infection rate below one episode per 1,000 catheter days is feasible and can be achieved without the use of antimicrobial agents

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