Review

# Clinical review: New technologies for prevention of intravascular catheter-related infections

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Published online: 29 September 2003
This article is online at http://ccforum.com/content/8/3/157

*Critical Care* 2004, **8:**157-162 (DOI 10.1186/cc2380)

## Abstract

Intravascular catheters have become essential devices for the management of critically and chronically ill patients. However, their use is often associated with serious infectious complications, mostly catheter-related bloodstream infection (CRBSI), resulting in significant morbidity, increased duration of hospitalization, and additional medical costs. The majority of CRBSIs are associated with central venous catheters (CVCs), and the relative risk for CRBSI is significantly greater with CVCs than with peripheral venous catheters. However, most CVC-related infections are preventable, and different measures have been implemented to reduce the risk for CRBSI, including maximal barrier precautions during catheter insertion, catheter site maintenance, and hub handling. The focus of the present review is on new technologies for preventing infections that are directed at CVCs. New preventive strategies that have been shown to be effective in reducing risk for CRBSI, including the use of catheters and dressings impregnated with antiseptics or antibiotics, the use of new hub models, and the use of antibiotic lock solutions, are briefly described.

**Keywords** catheter-related bloodstream infections, central venous catheters, new technologies, prevention

## Introduction

Intravascular catheters represent an essential part of the management of critically and chronically ill patients. However, their use is often complicated by serious infections, mostly catheter-related bloodstream infections (CRBSIs), which are associated with increased morbidity, duration of hospitalisation, and additional medical costs. The incidence of CRBSI varies considerably by type of catheter, frequency of catheter manipulation and patient-related factors, such as underlying disease and severity of illness [1]. However, the majority of CRBSIs are associated with central venous catheters (CVCs) [1], and in prospective studies the relative risk for CRBSI is up to 64 times greater with CVCs than with peripheral venous catheters [2–4].

Different measures have been implemented to reduce the risk for CRBSI, including use of maximal barrier precautions during catheter insertion, effective cutaneous antisepsis, and preventive strategies based on inhibiting micro-organisms originating from the skin or catheter hub from adhering to the catheter. Institution of continuous quality improvement programs, education and training of health care workers, and adherence to standardized protocols for insertion and maintenance of intravascular catheters significantly reduced the incidence of catheter-related infections and represent the most important preventive measures [1,2]. In the present review the new technologies for prevention of infections directed at CVCs, which have been shown to reduce the risk of CRBSI, including catheters and dressings impregnated with antiseptics or antibiotics, new hub models, and antibiotic lock solutions, are briefly described (Table 1).

For short-term CVCs (i.e. those in place <10 days), which are most commonly colonized by cutaneous organisms along the

CRBSI = catheter-related bloodstream infection; C-SS = chlorhexidine and silver sulfadiazine; CVC = central venous catheter; M-EDTA = minocycline and EDTA.

**Table 1**

**New technologies for the prevention of central venous catheter-related bloodstream infection**

| Technology | Usefulness | Grade* | Note |
|---|---|---|---|
| Antimicrobial impregnated dressings | | | |
| Chlorhexidine impregnated sponge dressing | Short-term CVCs | NR | Consider for CVCs expected to be in place for >5 days |
| Silver impregnated subcutaneous collagen cuff | Short-term CVCs | NR | Conflicting results in several clinical trials of efficacy |
| Antimicrobial impregnated catheters | | IB | Consider if institutional rate of CRBSI is high despite consistent application of preventive measures and CVC is expected to be in place for >5 days |
| Chlorhexidine–silver sulfadiazine impregnated catheters | Short-term CVCs | | Only the external surface of the CVC is coated. Not effective for CVCs left in place for >2 weeks |
| Minocycline–rifampin impregnated catheters | Short-term and long-term CVCs | | Both the internal and external surfaces of the CVC are coated. Prolonged antimicrobial activity |
| Hubs | | | |
| Catheter hub contained a iodinated alcohol solution | Long-term CVCs | NR | A recent trial failed to show any preventive benefit from the use of this hub |
| Povidone–iodine satured sponge | Long-term CVCs | NR | |
| Needleless connectors | | NR | Increased risk for CRBSI associated with improper use |
| Antimicrobial lock solutions | Long-term CVCs | II | Consider only for patients with recurrent CRBSIs despite consistent application of preventive measures |

*Adapted from the Centers for Disease Control and Prevention guidelines for the prevention of intravascular catheter-related infections [1]. Category IB: strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies, and a strong theoretical rationale. Category II: suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale. NR: no recommendations for or against use at this time. CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

external surface of the catheter, the most important preventive systems are those that decrease the extraluminal contamination. In contrast, with long-term CVCs (i.e. those in place >10 days), in which endoluminal spread from the hub appears to be the primary mechanism of infection, technologies that reduce endoluminal colonization in addition to extraluminal invasion of the catheter should provide additional protection against CRBSI.

## Method

This report is based on a literature review of published articles in the prevention of intravascular catheter-related infections. The review was conducted by searching the Medline database of the National Library of Medicine, Bethesda, MD, USA using the following key terms: catheter-related infections, catheter-related bloodstream infections, intravascular devices, central venous catheter, prevention, infection control practices, guidelines, and new technologies. The bibliographies of selected articles were also reviewed for pertinent studies.

## Antimicrobial impregnated catheters and dressings

### Chlorhexidine impregnated sponge dressing

A sponge dressing impregnated with chlorhexidine gluconate (BioPatch®; Johnson and Johnson, Arlington, TX, USA) applied at the insertion site of CVCs has been shown to reduce skin colonization and bacterial migration along the external surface of the catheter as compared with skin disinfection with povidone–iodine [5]. Therefore, it may be effective for the prevention of infections associated with short-term CVCs, in which extraluminal colonization is the primary mechanism of infection. However, local contact dermatitis to the BioPatch® dressing has been observed in low-birth-weight neonates, who require prolonged central access during the first 2 weeks of life [5].

### Silver impregnated subcutaneous collagen cuff

A silver impregnated collagen cuff attached to CVCs and left below the skin insertion site significantly decreased the risk

for extraluminal colonization associated with short-term catheters (mean duration of placement <10 days) [6,7]. The ionic silver has broad spectrum activity against bacteria and fungi, and the cuff provides a mechanical barrier to the migration of micro-organisms along the external surface of the catheter [1]. Nevertheless, clinical trials involving short-term CVCs have yielded conflicting results [6–9]. In two randomized clinical trials conducted in surgical patients assigned to receive a CVC with or without a silver cuff [7,8], the incidence of CRBSI was significantly greater in the control than in the cuffed catheter group (3.7% versus 1%). In the third clinical trial [9], however, no difference in the rates of catheter colonization or incidence of CRBSI was observed between patients who received and those who did not receive a silver cuffed CVC. Moreover, the cuff failed to reduce CRBSIs associated with catheters left in place for 20 days or longer [6,10,11]. This may be attributable to the biodegradable nature of the collagen and to the fact that the silver ions chelated to the cuff are released within 3–7 days. In addition, in this setting intraluminal spread from the hub is the dominant mechanism of catheter colonization. Another potential problem with the cuff is the protrusion of the system after insertion if the physician does not have sufficient experience with the insertion technique.

## Catheters impregnated with antimicrobial agents

Several studies have shown that CVCs impregnated with antiseptic or antibiotic agents decreased the risk for catheter colonization and CRBSIs [12–16] in comparison with unimpregnated catheters [14,15]. The best studied antimicrobial catheters are those impregnated with a combination of chlorhexidine and silver sulfadiazine (C-SS) or minocycline and rifampin [15,17].

### *Chlorhexidine and silver sulfadiazine impregnated catheters*

Catheters coated with C-SS have been shown to decrease the risk for colonization by twofold and the risk for CRBSI by at least fourfold compared with uncoated catheters [14]. The main limitations of these catheters is that only the external surface of the catheter is coated, thus conferring no protection from micro-organisms invading the internal surface of the catheter from contaminated hubs, and that the catheters have reduced antimicrobial activity and poor efficacy with long-term use (>2 weeks) [18–20]. Thus, these catheters have been shown to be particularly efficacious in reducing the risk for CRBSI associated with short-term CVCs [17] but failed to reduce the risk for CRBSI in situations requiring long-term catheterization [19]. In the largest clinical trial [19], which included 538 patients randomly assigned to receive a C-SS impregnated catheter or a nonimpregnated catheter, in which the mean duration of catheterization was 20 ± 12 days, no significant difference in the incidence of CRBSI was observed between the control group (4.7%) and the C-SS catheter group (5%) [19]. However, catheters impregnated intraluminally with chlorhexidine in addition to C-SS extraluminal impregnation are now available, and preliminary studies indicate their prolonged antimicrobial activity and improved efficacy in preventing infections [21].

C-SS impregnated catheters are more expensive than standard catheters, but they should reduce costs in settings in which the incidence of CRBSI is greater than 3.3 per 1000 catheter-days [14], despite adherence to other preventive strategies. A cost-effectiveness analysis concluded that using these catheters would decrease direct medical costs by US$196 per catheter inserted [17].

Resistance to the antiseptic components of this device has not been demonstrated in clinical studies [14]. There is concern about the potential anaphylaxis associated with the use of C-SS impregnated catheters, probably related to the chlorhexidine component, and 12 cases of anaphylactic reactions have been reported from Japan [22], and one case from the UK [23]. However, there have been no reports of such reactions from the USA, where more than 3 million catheters were sold during 2000 [24].

### *Minocycline–rifampin coated catheters*

Catheters coated with minocycline–rifampin have the advantage of coating both the internal and external surfaces of the catheters, and have been associated with a lower rate of infection than have C-SS impregnated catheters. In a prospective clinical trial in which patients were randomly assigned to receive either minocycline–rifampin or C-SS catheters, the rate of CRBSI was significantly lower in the former group than in latter group (0.3% versus 3.4%) [25]. Indeed, catheters coated with minocycline–rifampin exhibited broad spectrum inhibitory activity both *in vitro* and *in vivo* against Gram-positive bacteria, Gram-negative bacteria, and *Candida albicans* that was significantly superior to that with C-SS impregnated catheters [20]. Moreover, the antibiotic activity of minocycline–rifampin is retained for longer periods *in situ* [15,20,25,26]. Although more expensive than C-SS impregnated catheters, a recent analysis suggested that CVCs coated with minocycline–rifampin are cost-effective for patients catheterized for at least 1 week and lead to overall cost savings when patients are catheterised for 2 weeks or longer [27].

Although no resistance to the antimicrobial components of these devices has been demonstrated in clinical studies [15,25], an *in vitro* study demonstrated a 10- to 16-fold increase in the minimal inhibitory concentration of the minocycline–rifampin combination with respect to *Staphylococcus epidermidis*, suggesting that resistance to this combination can develop. The study also indicated that minocycline had a protective role against development of rifampin resistance, because resistance to rifampin increased only 80-fold when rifampin was used in combination with minocycline, in contrast to 25 000-fold when rifampin was used alone [28]. However, a thorough investigation is required to determine the risk for emergence of resistance to minocycline–rifampin associated with long-term use of these catheters.

*Polyurethane catheters*

Polyurethane catheters combined with silver, carbon and platinum (oligon-treated catheters) represent a new option for the prevention of CRBSI. In a prospective randomized trial, Ranucci and coworkers [29] compared the rates of CVC colonization and CVC bloodstream infections between 268 patients with an oligon-treated catheter and 277 patients with a polyurethane catheter treated with benzalkonium chloride. Patients in the oligon group demonstrated a lower risk for catheter colonization (relative risk 0.63, 95% confidence interval 0.46–0.86; $P=0.003$), whereas no significant differences in CVC bloodstream infections were found between the oligon and the control groups.

*Silver iontophoretic device*

Another technology is the silver iontophoretic device, in which silver ions are released through a low voltage current to carbon-impregnated CVCs [30] or through silver wires that are attached to the proximal segment of a silicone catheter [31]. Although this technology has been shown to prevent catheter infections [20,31], the clinical safety and efficacy of this device have not been demonstrated.

## Hubs and needleless connectors

### Catheter hub containing a iodinated alcohol solution

A catheter hub containing an antiseptic chamber filled with 3% iodinated alcohol has been shown to reduce the rate of CRBSIs by fourfold compared with a standard hub model [32]. This model will be most useful with long-term CVCs, in which hub and lumen colonization are the leading causes of CRBSI. On the other hand, a recent clinical trial failed to show any benefit from the use of this hub in preventing CRBSI [33].

### Povidone–iodine saturated sponge

Another model, which uses a povidone–iodine connection shield to encase the catheter hub, showed a significant reduction in the rate of CRBSI as compared with a control hub (0% versus 24%; $P<0.05$) in a randomized controlled clinical trial involving patients receiving total parenteral nutrition [34].

### Needleless connectors

The use of needleless intravenous access devices, introduced to reduce the risk associated with occupational exposure of health care workers to blood-borne pathogens [35], was associated with an increased rate of CRBSI [36–38], which may be related to improper handling and inaccurate use of these devices [39]. However, the potential for needleless connectors to increase the risk for CRBSI is uncertain, and recent clinical trials have shown that these devices do not increase the risk for infection [40] when they are used correctly and in combination with rigorous aseptic techniques.

## Antimicrobial lock solution

Antimicrobial lock is a novel technique in which an antimicrobial solution, often consisting of an anticoagulant along with an antibiotic agent, is instilled into the lumen of the catheter and allowed to remain for a defined period, usually 6–12 hours, after which it is removed. Antimicrobial lock solutions have shown to be mostly effective for the prevention of infections associated with long-term CVCs [41,42] but they could also be useful in short-term catheters [43].

Various antimicrobial agents have been shown to be efficacious in reducing the risk for infection, including vancomycin–heparin and vancomycin–ciprofloxacin–heparin solutions [42,44]. Because the use of vancomycin is an independent risk factor for the acquisition of vancomycin-resistant enterococci [45], this practice is not recommended for routine use [1]. However, in individual cases in which a patient requires indefinite vascular access but continues to experience CRBSIs despite rigorous observance of infection control measures, the use of vancomycin lock solution to preserve vascular access should be considered. A novel lock solution consisting of minocycline and EDTA (M-EDTA) has also been shown to have antimicrobial activity against the most common organisms associated with CRBSI, including Gram-positive and Gram-negative bacteria and *Candida albicans*, resulting in prevention of infection [46]. In a prospective cohort study, M-EDTA proved to be efficacious in preventing port-related infections without causing any adverse events [47]. However, randomized clinical trials are needed to test further the ability of M-EDTA to prevent long-term CVC infections.

## Prophylactic thrombolysis

Prophylactic use of anticoagulant agents, including heparin or warfarin, reduced the incidence of catheter thrombosis [20,41,42]. Because thrombi could serve as a nidus for microbial colonization of CVCs [48,49], the use of anticoagulants may have a role in the prevention of CRBSI. For example, in a double-blind randomized controlled study conducted in a pediatric intensive care unit, heparin bonding was associated with a significant reduction in the incidence of infection (4% and 33% in heparin-bonded and non-heparin-bonded CVCs, respectively) [50]. Furthermore, in a meta-analysis evaluating benefit of heparin prophylaxis (doses of 3 U/ml total parenteral nutrition, 5000 U every 6 or 12 hours, or 2500 U of subcutaneous low-molecular-weight heparin every day) in patients with CVCs, the risk for catheter-related central venous thrombosis was reduced with the use of prophylactic heparin [51]. The meta-analysis also found a significantly decreased risk for bacterial colonization of the catheter and an associated reduction in CRBSI with use of heparin; however, studies included used variable definitions of catheter-related infections and the findings require confirmation by trials adhering to current, stricter definitions.

## Future directions

A better understanding of the pathogenesis of CVC-related infections should lead to the development of more effective preventive strategies, including antiseptics with greater and more prolonged antimicrobial activity, and new materials that

make CVCs intrinsically resistant to microbial colonization and that do not promote antimicrobial resistance. Because of its critical role in the infection process, bacterial adherence represents a potential target for the development of new preventive strategies, and agents that can block the process of adherence, such as specific bacterial surface adhesin-blocking antibodies, may prove to be effective at preventing infections. *In vitro* studies have been conducted to assess the effectiveness of new polymer–antibiotic systems in inhibiting bacterial biofilm formation [52] and in reducing neutrophil activation after surface contact on different biomaterials, thus reducing the risk for biomaterial-mediated inflammatory reactions [53]. Moreover, organisms such as staphylococci, *Candida* spp. and some others produce a microbial biofilm that helps them to survive on the surfaces of foreign bodies in the bloodstream. The development of biofilm involves intercellular signaling molecules that serve in a communication system termed quorum sensing. Quorum sensing enables population density control of gene expression [54]. Molecules that inhibit quorum sensing signal generation among organisms could block microbial biofilm formation and prevent catheter colonization [55].

## Conclusion

CRBSIs, as a consequence of the use of CVCs, are associated with significant morbidity, mortality and additional medical costs. Nevertheless, most CVC-related infections are preventable, and preventive strategies should aim at achieving maximal antiseptic barrier precautions during catheter insertion, catheter site maintenance, and hub handling. However, new technologies that have already been proven to be effective in clinical trials in preventing CVC infections, particularly those intended for short-term use, should be considered in clinical practice. Moreover, many of these new technologies have proven to be not only effective but also cost-effective.

## Competing interests

None declared.

## Acknowledgements

The work of the authors is supported by grants from Ricerca Corrente e Finalizzata, Ministry of Health and from Programma Nazionale di Ricerca sull'AIDS, Istituto Superiore di Sanità, Italy.

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