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# Reducing the risk of infection associated with vascular access devices through nanotechnology: a perspective

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**Abstract:** Intravascular catheter-related infections are still a major problem in health care and are associated with significant morbidity, mortality, and additional cost. The formation of microbial biofilm on catheters makes these infections particularly complicated, as microbial cells that detach from the biofilm can lead to infection, and because these microorganisms are highly resistant to many antimicrobial agents; thus, catheter removal is often required to successfully treat infection. To reduce the risks of catheter-related infections, many strategies have been applied, such as improvements in aseptic insertion and post-insertion care practices, implantation techniques, and antibiotic coated or impregnated materials. However, despite significant advances in using these methods, it has not been possible to completely eradicate biofilm infections. Currently, nanotechnology approaches seem to be among the most promising for preventing biofilm formation and resultant catheter-related bloodstream infection (especially with multi-resistant bacterial strains). In this review, current knowledge about catheter technology and design, the mechanisms of catheter-related bloodstream infection, and the insertion and care practices performed by medical staff, are discussed, along with novel, achievable approaches to infection prevention, based on nanotechnology.

**Keywords:** catheter related infections, biofilm, nanotechnology

## Introduction

Intravascular catheter- (IVC-) related infections lead to high morbidity and mortality for patients, and increase costs of health care.<sup>1</sup> Infections develop when microorganisms adhere to catheter surfaces and produce extracellular substances that facilitate adhesion (and provide a structural matrix) for forming biofilms.<sup>2</sup> Following biofilm development, microbial cells from the biofilm mature and can periodically disperse into the bloodstream, causing serious infections.<sup>2</sup> Biofilms are resistant to host defence mechanisms and antibiotic agents, making the treatment of catheter-related infections more challenging. In order to prevent catheter-related infections, a large number of strategies and approaches have been developed, including strict hygienic procedures during catheter insertion and use; total or partial (tunneling) implantation of long-term catheters; surface modification of catheter biomaterials with antimicrobial coatings or impregnation; and antibiotic or antimicrobial locking solutions.<sup>2</sup> However, it remains impossible to achieve a completely anti-adhesive catheter material since catheter surfaces can be rapidly covered by plasma and matrix proteins, on which bacteria display specific adhesions. The challenge of biofilm-related infections remains. Nanotechnologies, especially nanomaterials, are one of the more promising new strategies that aim to prevent biofilm infections in patients with IVCs.

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This review will summarize current knowledge about catheter-related bloodstream infections (CRBSIs), as well as the nanotechnologies in use, or in development, to prevent catheter-related infections occurring due to colonization and/or biofilm formation on catheter surfaces. We also discuss the knowledge gained from microbial research in other medical and non-medical applications that may be helpful to understanding the IVC context. In addition, published theories and data regarding microbial colonization and biofilm development, specifically related to IVCs, are reviewed. This review aims to provide baseline information for the future development of new and effective strategies to prevent catheter-related infections.

## Catheter technologies and catheter design

Intravenous catheters have evolved considerably, from the early prototypes of goose quill, silver, glass, and steel tubes, to modern day polyurethane- and silicone-based models. The ideal catheter exhibits a high tensile strength, is soft and pliable, inherently chemical-resistant, biocompatible, and meets flow requirements. Common catheter materials include polyurethane, silicone, polyethylene and Teflon®. A comparison of the relevant characteristics of these catheter materials is shown in Table 1. Polyurethane catheters are now often the preferred material. They are highly biocompatible (therefore, well-tolerated by patients), compatible with the majority of drugs, and resistant to many chemicals.<sup>3</sup> Nevertheless, the repeated application of alcohol-based cleaning agents potentially can perish the catheter. Polyurethane is thromboresistant, and softens within the body. Therefore, mechanical trauma and irritation within the vein are reduced, compared against harder materials.<sup>4</sup> Other advantages of polyurethane are its tensile strength, multiple lumens, and smaller external diameters, which maximize blood flow in a vessel with catheter. Modern polyurethane catheters are now available as semirigid yet flexible materials, often used for short-term catheter access.

They are sufficiently stiff for percutaneous insertion over a wire without splitting the sheath, yet soften in the body after insertion. Silicone catheters are also biocompatible and compatible with most drugs, as well as alcohol-based cleaning solutions, although they can be damaged by peroxide and some povidone-iodine solutions. Silicone is soft, pliable, and thromboresistant,<sup>4</sup> but it has limited tensile strength, resulting in easy rupture, and it requires a restricted infusion flow pressure.<sup>5</sup> Silicone catheters need insertion through a sheath or cannula. Other IVC materials such as polyethylene and Teflon® (tetrafluoroethylene-hexafluoropropylene) are less favorable catheter materials, and have nearly been replaced by polyurethane and silicone, since they are less biocompatible, stiffer, and have poor flexibility.<sup>4</sup> Teflon has also been shown to have higher infection rates, compared against the other three catheter materials.<sup>6</sup>

There are numerous types of IVC, with varying designs, for different functional requirements and durations of use. Short-term central venous catheters are usually made of polyurethane.<sup>7</sup> They are relatively short tapered, open-ended multilumen catheters, used for 3–10 days. Long-term central venous catheters may be used for months or years, and have a catheter portion “tunneled” or “cuffed” under the skin. Alternatively, totally implanted “ports” may be implanted into a central vein, and periodically accessed using a needle, for long-term therapy. Small, peripheral venous or arterial catheters are single lumen, and are also commonly made of polyurethane. Midline catheters are single or dual lumen, predominantly composed of silicone, and are used for 2–4 weeks.<sup>8</sup> Peripherally-inserted central catheters (PICCs) can be made of polyurethane or silicone, with single to triple lumen types available. They are recommended for mid-term therapy: from 6 weeks to 1 year.<sup>9</sup> PICCs can be valved or non-valved. Non-valved PICCs are open-ended and require regular positive flushing after use, to prevent blood backflow causing occlusion.<sup>10</sup> Valved PICCs contain a pressure-sensitive valve at the side of the distal end, which allows both fluid infusion and blood aspiration;<sup>10</sup> therefore,

**Table 1** Comparison of catheter material characteristics

	Polyurethane	Silicone	Polyethylene	Teflon®
Biocompatibility	Excellent	Excellent	Fair	Fair
Stiffness	Softens in body	Soft	Stiff	Stiff
Ease of insertion	Difficult	Fair	Easy	Easy
Ease of modifying	Fair	Easy	Difficult	Difficult
Tensile strength	Excellent	Fair	Excellent	Excellent
Flexibility	Fair	Excellent	Poor	Poor
Coefficient of friction	Excellent	Fair	Good	Excellent
Infection rate	Low	Fair	High	High

heparinized flushes are not required. Hemodialysis catheters are composed of silicone or polyurethane and can be cuffed, or non-cuffed, depending on the duration of usage. These catheters have large bores and relatively stiff constructions, to avoid wall collapse under negative pressure from pumped systems.<sup>11</sup> The lumen has one end-hole and multiple side holes, to improve flows and mixing of blood. Two functionally separate catheters can be inserted in parallel, their tips lying slightly separated, in the same vein.<sup>11</sup> Alternatively, a combined dual or triple lumen catheter can be used, which has a staggered design: one lumen positioned 3–5 cm above the other, to prevent recirculation of treated blood. To prevent thrombotic events occurring within this type of catheter, heparin locks are essential. Late catheter malfunction is often the consequence of fibrin deposition around the catheter tip – an unpredictable process, but one that occurs more frequently in some patients and less frequently in others.<sup>11</sup>

## Catheter-related bloodstream infection

The use of IVCs is essential for the successful management of critically and chronically ill patients.<sup>12</sup> However, CRBSIs have become a leading cause of health care-associated bloodstream infections, and are associated with substantial morbidity and mortality.<sup>13</sup> More than 250,000 CRBSIs occur annually in the USA, with an attributable mortality ranging from 12%–25% in critically ill patients, and with an added cost ranging from US\$4,000–\$56,000.<sup>14,15</sup>

CRBSI is defined as 1) fever and other clinical manifestations of bloodstream infection in a patient with an IVC; 2) the presence of positive simultaneous quantitative blood cultures from the IVC and the peripheral vein, yielding the

same organism; 3) no apparent source for the bloodstream infection, other than the catheter; and 4) positive semi-quantitative catheter tip cultures with  $\geq 15$  colony forming units (CFUs) of the same microorganisms as isolated from the blood cultures. Alternatively, CRBSI can be diagnosed through simultaneous quantitative blood cultures, whereby the number of colonies isolated from the blood drawn through the IVC is at least three times greater (ratio:  $\geq 3:1$ ) than the number of colonies isolated from blood drawn via a peripheral vein, or from one of two different lumen-drawn blood cultures from multi-lumen catheters (“possible CRBSI”).<sup>1</sup> The differential between time-to-positivity of peripherally-drawn blood cultures of  $\geq 2$  hours growth, and simultaneously drawn peripheral venous blood cultures, is also diagnostic of CRBSI.<sup>1</sup>

CRBSI most frequently develops in seriously ill patients admitted to hematology-oncology and intensive care units (ICUs) of acute care hospitals. The most commonly reported causative pathogens for CRBSI are coagulase-negative staphylococci, *Staphylococcus aureus*, enterococci, and *Candida* spp. (Table 2).<sup>16,17</sup> According to the US Centers for Disease Control and Prevention’s database, approximately 19% of CRBSI cases involve gram-negative bacilli.<sup>18</sup> Antimicrobial resistance is a concern with all pathogens responsible for CRBSIs. It has been demonstrated that methicillin-resistant *S. aureus* (MRSA) accounts for more than 50% of all *S. aureus* isolated in ICUs – although the incidence of CRBSI caused by skin organisms (particularly MRSA) in ICUs has decreased in recent years, due to coordinated efforts in many countries to improve sterile insertion procedures to prevent insertion-related contamination of central venous catheters.<sup>16,17</sup> By contrast, with regard to gram-negative rods,

**Table 2** Incidence rates of most commonly isolated pathogens from MNBSIs, and associated crude mortality rates, for patients in ICU and non-ICU wards 17

Pathogen	CRBSI per 10,000 admissions	Percentage of CRBSI			Crude mortality (%)		
		Total (n=20,978)	ICU (n=10,515)	Non-ICU ward (n=10,442)	Total	ICU	Non-ICU ward
Coagulase-negative <i>Staphylococcus</i>	15.8	31.3	35.9	26.6	20.7	25.7	13.8
<i>S. aureus</i>	10.3	20.2	16.8	23.7	25.4	34.4	18.9
<i>Enterococcus</i> spp.	4.8	9.4	9.8	9.0	33.9	43.0	24.0
<i>Candida</i> spp.	4.6	9.0	10.1	7.9	39.2	47.1	29.0
<i>Escherichia coli</i>	2.8	5.6	3.7	7.6	22.4	33.9	16.9
<i>Klebsiella</i> spp.	2.4	4.8	4.0	5.5	27.6	37.4	20.3
<i>Pseudomonas aeruginosa</i>	2.1	4.3	4.7	3.8	38.7	47.9	27.6
<i>Enterobacter</i> spp.	1.9	3.9	4.7	3.1	26.7	32.5	18.0
<i>Serratia</i> spp.	0.9	1.7	2.1	1.3	27.4	33.9	17.1
<i>Acinetobacter baumannii</i>	0.6	1.3	1.6	0.9	34.0	43.4	16.3

**Abbreviations:** MNBSI, monomicrobial nosocomial blood stream infection; ICU, intensive care unit; CRBSI, catheter-related bloodstream infection.

the incidence of antimicrobial resistance to third-generation cephalosporins among *Klebsiella pneumonia* and *Escherichia coli* is increasing significantly, along with imipenem and ceftazidime resistance among *Pseudomonas aeruginosa*.<sup>18</sup>

It is believed that there are four pathways for bacteria to enter into the sterile bloodstream and cause catheter-related infections.<sup>16</sup> The first is extraluminal contamination of the catheter with skin organisms, occurring during insertion, or migration of such organisms down the catheter tract while it is in place. This is the most common infection route for short-term catheters. The second route is intraluminal, involving contamination of catheter hubs and connectors through contact with the hands of hospital staff who use the catheter to install medicine or take blood. The third route is direct contamination of the catheter by bacteria circulating in the bloodstream; for example, following translocation of gastrointestinal flora through the intestinal wall. The fourth pathway is through contaminated infusate, which may occur at the manufacturing stage (intrinsic contamination), or during manipulation by health care staff when preparing or administering fluids (extrinsic contamination).

If contamination occurs, the initial microbial attachment of bacteria onto the inner and outer surfaces of IVCs is almost inevitably followed by biofilm development and maturation, which is followed by dispersion of microbial cells from the biofilm into the bloodstream, causing CRBSI. Microorganisms embedded in biofilms typically present phenotypic and genotypic characteristics different to those grown planktonically.<sup>19</sup> They are able to obtain and concentrate a number of different nutrients from the environment.<sup>19</sup> They are resistant to a number of antimicrobial agents, not only because the antimicrobials cannot penetrate into all the biofilm layers, but also because the organisms grow slowly and may then be resistant to immune defence mechanisms.<sup>20</sup> The biofilm mode can also facilitate dissemination of organisms. Furthermore, microorganisms may exhibit different virulence phenotypes when growing within a biofilm; these phenotypes may not have been detected from IVCs in the past, because traditional hospital diagnostic tests, such as the semiquantitative roll-plate technique, used to culture catheter tip segments, involve growth of organisms on rich nutrient media, under planktonic conditions.<sup>21</sup> Rather than being amorphous aggregates, biofilms are complex, structured communities in which physiological conditions, such as nutrient and oxygen availability, vary at different depths.<sup>22</sup> Therefore, the microorganisms at different depths are phenotypically, morphologically, and functionally different. Once biofilm infection occurs, the host will

establish an immune response to antigens released from the biofilm. However, not only may the host's immune system fail to eradicate the biofilm, it may also result in damage to surrounding tissues.

The pathogenesis of fibrin sheath formation from biofilms is still not understood. After biofilm formation, fibrin and many other molecules, such as laminin, collagen, and even muscle cells, convert the biofilm to a mature sheath.<sup>23</sup> Metallic cations, such as magnesium, calcium, and iron, may stabilize the biofilm and facilitate biofilm development and bacterial growth.<sup>24</sup> Catheter thrombosis on the fibrin sheath may be facilitated by platelet activation, decreased levels of protein C and antithrombin III, hyperfibrinogenemia, and homocysteine elevation. It has been demonstrated that the presence of catheter-related thrombosis increases the risk of CRBSI.<sup>25,26</sup> Many patients require long-term IVCs, and attempts have been made to treat CRBSI without removing the IVC, with variable results. However, as understanding of biofilm structure and function develops, it is clear why often the only solution to an infected IVC is catheter removal, which brings increased hospital costs, additional painful invasive procedures for patients, and interruption to medical therapy.

There are numerous recommended preventive strategies for clinicians to avoid CRBSIs, and these are supported by varying levels of evidence for their effectiveness. Strategies include issues of education, training, and staffing among health care providers who insert and maintain IVCs; selection of catheters and sites; hand hygiene and aseptic technique; maximal sterile barrier precautions on insertion; pre-insertion skin preparation; catheter site dressing regimens; patient cleansing (bathing); catheter securement devices; antimicrobial/antiseptic impregnated catheters (for >5 day catheters, if other education-based interventions have not been effective); antibiotic/antimicrobial ointments for dialysis catheter sites; antimicrobial lock solutions for patients with repeated CRBSI and long-term IVCs; at least weekly replacement of IV infusion tubing; disinfection of needleless connectors prior to use; and replacement of connectors at least every 72 hours.<sup>16</sup>

The majority of recommended CRBSI prevention strategies target improved clinical practices among hospital staff, rather than technological approaches. The most successful development in recent years has been the implementation of central venous catheter "care bundles", which are quality campaigns targeting CRBSI in ICUs. Such initiatives comprise simultaneous implementation, and focus on consistent use of, five best practice procedures, in the context

of key stakeholder championship, with ongoing audit and feedback of infection rates to staff. Numerous national and international campaigns have been launched, stemming from the successful Keystone ICU Project in Michigan, USA.<sup>27</sup> The bundles focus predominantly on the insertion procedure, including hand hygiene and maximal sterile barrier precautions by the inserter; decontamination of the skin site pre-insertion (with 2% chlorhexidine gluconate in 70% alcohol); avoidance of the femoral insertion site, if possible; and removal of unnecessary IVCs. It is widely agreed that such campaigns have greatly reduced, but not eliminated, CRBSIs, particularly those stemming from extra-luminal contamination, occurring during the insertion procedure.<sup>16</sup> There is a resultant need to now focus on maintaining those successful infection-prevention practices, and extending them outside of the ICU setting, while adding improvements in post-insertion care, to focus on intraluminal colonization-related infections.<sup>28</sup>

## Nanotechnology

The foundation material of the IVC can also be coated or impregnated with antibiotic or antiseptic agents, to reduce the risk of CRBSIs. Despite significantly higher initial purchase costs, such catheters have been associated with an overall decrease in hospital costs associated with treating CRBSIs. Comparing infection rates of non-impregnated

and impregnated catheters, results indicate that impregnation could reduce catheter-related infection rates in various settings and countries (Table 3). However, concerns exist about the potential for development of antimicrobial/antibiotic resistance. Currently, antiseptic/antibiotic catheters are only recommended for short-term use if the CRBSI rate does not decrease, despite adherence to basic prevention measures.<sup>29</sup> While antiseptic/antibiotic-impregnated intravascular catheters have been shown to decrease the rate of CRBSI in patients with short-term catheters, the benefit in patients with long-term catheters remains unclear. There is additional concern about the potential to generate multidrug-resistant organisms. In all, none of these strategies seems able to totally prevent CRBSIs; nanotechnology might bring new hope.

The use of antimicrobial agents was extended to IVC dressing. In one randomized multicenter assessor-blind trial, 1,636 patients with catheter dressings, with or without chlorhexidine-impregnated sponges as part of the standard, transparent, semipermeable polyurethane IVC dressing, were evaluated.<sup>30</sup> A total of 3,778 catheters were enrolled (28,931 catheter-days). The chlorhexidine-impregnated sponge dressings decreased rates of major catheter-related infections (0.6 per thousand catheter-days versus [vs] 1.4 per thousand catheter-days; hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.17–0.93

**Table 3** Rates of catheter-related colonization and bloodstream infection associated with non-impregnated and antiseptic/antibiotic-impregnated intravascular catheters

Catheter type	Study	Country	Setting	Number	Catheter colonization	Catheter-related bloodstream infection	
Non-impregnated	Hanna et al <sup>37</sup>	USA	Single center	174	n/a	14 (8.0%) <sup>a</sup>	
	Ostendorf et al <sup>34</sup>	Germany	Single center	94	31 (33%)	7 (7%) <sup>b</sup>	
	Jaeger et al <sup>102</sup>	Germany	Single center	55	9 (16.4%)	8 (14.5%) <sup>c</sup>	
	Sheng et al <sup>103</sup>	Taiwan	Single center	122	25 (20.5%)	2 (1.6%) <sup>d</sup>	
	Lorente et al <sup>104</sup>	Spain	Single center	287	n/a	12 (4.18%) <sup>e</sup>	
Impregnated with	Silver sulfadiazine/chlorhexidine	Walder et al <sup>133</sup>	Switzerland	Multiple centers	1,544	n/a	65 (4.2%)
		Ostendorf et al <sup>34</sup>	Germany	Single center	90	11 (12%)	3 (3%) <sup>b</sup>
		Jaeger et al <sup>102</sup>	Germany	Single center	51	5 (9.8%)	1 (1.96%) <sup>c</sup>
	Minocycline/rifampin	Darouiche et al <sup>36</sup>	USA	Multiple centers	382	87 (22.8%)	13 (3.4%) <sup>f</sup>
		Darouiche et al <sup>36</sup>	USA	Multiple centers	356	28 (7.9%)	1 (0.3%) <sup>f</sup>
		Hanna et al <sup>37</sup>	USA	Single center	182	n/a	3 (1.65%) <sup>a</sup>
		Sheng et al <sup>103,d</sup>	Taiwan	Single center	113	9 (7.1%)	1 (0.9%) <sup>d</sup>
		Lorente et al <sup>104</sup>	Spain	Single center	238	n/a	0 <sup>e</sup>

**Notes:** <sup>a</sup>Odds ratio for CRBSI (catheter-related bloodstream infection): 0.1 for minocycline/rifampin, compared against non-impregnated catheters;  $P < 0.001$ ; <sup>b</sup>odds ratio for colonization: 0.36 silver sulfadiazine/chlorhexidine-impregnated, compared against non-impregnated catheters;  $P = 0.01$ . No significant differences for CRBSI; <sup>c</sup>odds ratio for colonization: 0.46 silver sulfadiazine/chlorhexidine-impregnated, compared against non-impregnated catheters;  $P = 0.035$ . Odds ratio for CRBSI: 0.12 silver sulfadiazine/chlorhexidine-impregnated, compared against non-impregnated catheters,  $P = 0.02$ ; <sup>d</sup>odds ratio for colonization: 0.34 silver sulfadiazine/chlorhexidine-impregnated, compared against non-impregnated catheters;  $P = 0.006$ . No significant differences for CRBSI; <sup>e</sup>odds ratio for CRBSI: 0.13 for minocycline/rifampin, compared against non-impregnated catheters;  $P < 0.05$ ; <sup>f</sup>odds ratio for colonization: 0.31 for minocycline/rifampin, compared against silver-sulfadiazine/chlorhexidine impregnated catheters;  $P < 0.001$ . Odds ratio for CRBSI: 0.08 for minocycline/rifampin, compared against silver-sulfadiazine/chlorhexidine impregnated catheters;  $P < 0.0001$ .

**Abbreviation:** n/a, not available.

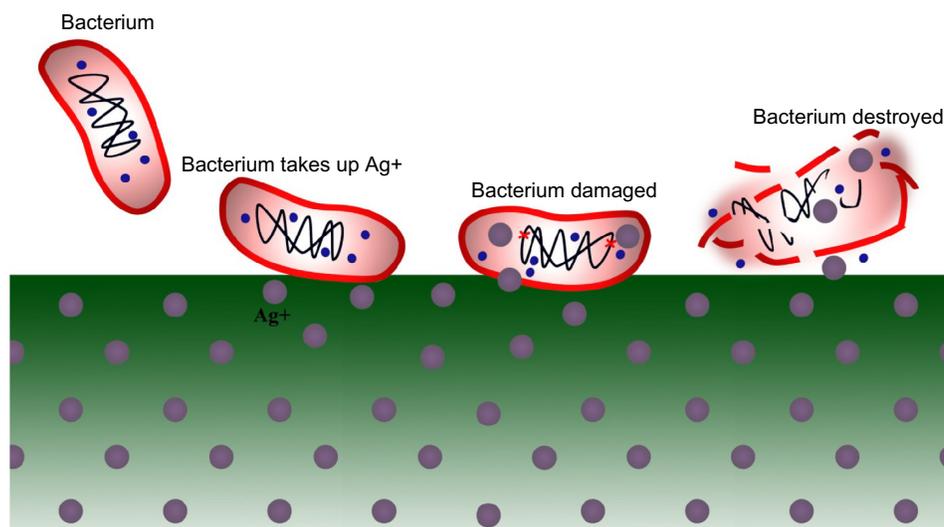
per thousand catheter-days;  $P=0.03$ ) and CRBSIs (0.40 per thousand catheter-days vs 1.3 per thousand catheter-days; HR, 0.24; CI, 0.09–0.65 per thousand catheter-days;  $P<0.001$ ).<sup>30</sup> A randomized controlled study of a chlorhexidine-impregnated sponge dressing in 74 children showed that it could reduce the rates of catheter colonization (HR, 0.61; CI, 0.3716–1.023;  $P=0.0446$ ), but there was no statistical difference in CRBSIs when compared with no antimicrobial dressings.<sup>31</sup> One possible reason is that the study was underpowered to detect these differences.

Catheters whose outer surfaces are impregnated with chlorhexidine and silver sulfadiazine have been confirmed to reduce the risks of CRBSIs.<sup>32</sup> They remained effective when the median duration of insertion time was less than 7 days (median, 6 days; interquartile range [IQR] 5.2–7.5 days) compared with control catheters (median 12 days; IQR 7.8–20 days).<sup>33</sup> Second-generation catheters are manufactured with chlorhexidine coating on the internal surfaces, extending into the extension set and hubs, while the external luminal surface is coated with chlorhexidine and silver sulfadiazine.<sup>34,35</sup> Although it has been shown that second-generation catheters can reduce catheter colonization, a significant decrease of the CRBSI rate was not detected.<sup>34,35</sup> Catheters impregnated with minocycline and rifampin on external and internal surfaces were associated with lower risks of CRBSI, compared against catheters with external coating of chlorhexidine and silver sulfadiazine.<sup>36</sup> Silicone catheters impregnated in both the external and internal surfaces with a combination of minocycline and rifampin can decrease the rate of CRBSIs, compared against controls, even with an average dwell time of 60 days.<sup>37</sup> No correlation has been shown between the usage of minocycline- and rifampin-

impregnated catheters and the development of antimicrobial resistance, or the selection of resistant flora.

Thrombus proteins can also increase bacterial attachment on IVCs, and have been associated with CRBSIs. It has been shown that the formation of a fibrin sheath around the catheter greatly increases catheter colonization.<sup>38</sup> Heparin-coated catheters were reported to be able to decrease thrombosis, and the risks of CRBSIs.<sup>39</sup> However, the potential benefits of heparin, or heparin-coated catheters, must be balanced against the small, but important, risk of heparin-induced thrombocytopenia. Because heparin solutions contain preservatives with antimicrobial activity, it is unknown whether a decrease in the CRBSI rate is due to decreased thrombus formation, or due to the preservative.

Many metal ions have antimicrobial activity. Among these, silver has the highest level of toxicity for microorganisms and the lowest toxicity for animal cells.<sup>40</sup> Silver nanoparticles are clusters of silver atoms that exhibit strong bactericidal activity, against both gram-positive and gram-negative bacteria.<sup>41</sup> Silver ions can inhibit replication of bacteria (through binding to the microbial DNA) and/or switch off important enzymes, leading to microbial death (Figure 1).<sup>42</sup> It has also been suggested that silver nanoparticles could prevent biofilm formation, since they have an affinity for proteinaceous compounds, where they combine with the sulfhydryl group, inducing protein denaturation and corresponding enzyme inactivation.<sup>43</sup> As yet, silver nanoparticles have not been shown to cause microbial resistance, in contrast to increasing microbial resistance towards many traditional antimicrobial agents, and the consequent development of resistant strains. A possible explanation is



**Figure 1** Mechanisms of silver ions against bacterium.

that silver nanoparticles do not only exert their antibacterial effects at a particular site, but at several locations, such as the bacterial wall, during proteosynthesis, and in DNA.<sup>41</sup> Silver nanoparticle-coatings could exert their antimicrobial properties in vivo, by slowly releasing silver ions.<sup>44</sup> Silver nanoparticles enable a constant local supply of silver ions at the coating–tissue interface, and also allow improved contact with the microorganisms.<sup>45</sup> Therefore, the prevention of microbial adhesion and biofilm formation is more prolonged than with other antimicrobial approaches. Thus, IVC coating with silver nanoparticles could protect both outer and inner surfaces of catheters through continuous release of silver ions, to provide antimicrobial activity.

In addition to use in catheters, nanotechnology offers promise in reducing post-insertion intraluminal IVC colonization related to staff handling of IVC needleless connectors. Needleless connectors are used to cap off IVCs temporarily not in use, to connect infusion administration sets to the catheter, and to provide an access point for administration of medicines and withdrawal of blood specimens. Recently, connector devices have increasingly attracted the attention of commercial manufacturers and researchers alike.<sup>46</sup> Many such devices have recently entered the market, with a variety of internal engineering. Some needleless connectors incorporate a valve, to prevent backflow of blood and intravenous fluids into the connector, which aims to prevent catheter occlusion or thrombosis.<sup>47,48</sup> However, many studies suggest that some valved needleless connectors actually increase the risk of CRBSI. Jarvis et al compared split septum needleless connectors against mechanical valve-type needleless connectors, and demonstrated that mechanical valve needleless connectors have higher CRBSI rates, despite similar bloodstream infection surveillance, definitions, and prevention strategies.<sup>49</sup> One investigation found CRBSIs increased after a switch from a negative fluid displacement to a positive displacement mechanical valve.<sup>50</sup> However, in another observational study, a switch from a negative displacement mechanical valve to a different, luer-activated positive displacement mechanical valve led to a significant decrease in CRBSIs.<sup>51</sup> Definitive reasons for these sometimes conflicting results with different types of needleless connectors are still unknown. Regardless of their make, frequent handling, and accessing of catheter hubs by staff, needleless connectors and injection ports have great potential to put patients at risk of primary bloodstream infections, since they facilitate entry of bacteria into the connector and fluid path.<sup>52</sup> Research from Donlan et al showed a high incidence of biofilm formation on the interior surface of valved connectors that had been used clinically.<sup>53</sup>

As a consequence, increasing numbers of studies are being added to the literature on reducing CRBSIs, related to use of needleless connectors. It has been shown that external disinfection of the devices with chlorhexidine/alcohol, rather than alcohol alone, can reduce IVC colonization.<sup>47,54</sup> In addition, the time spent on applying the disinfectant is important. Results from one study suggest that wiping the connector with 70% isopropyl alcohol for 3–5 seconds did not adequately disinfect the septal surface.<sup>55</sup> Many studies have also shown that conventional disinfection may not be able to prevent entry of microorganisms, if significant contamination of the membranous septum is present prior to the injection or infusion of fluids.<sup>56,57</sup>

A novel silver nanoparticle-coated connector has been introduced recently. Designed as a single use, disposable valved connector, it is constructed of polycarbonate. However, with the exception of the silicone membranous septum, the entire surface of the connector, including the entirety of the internal fluid path and the external casing, has a silver nanoparticle coating.<sup>46</sup> Silver nanoparticles are stably imbedded in the polycarbonate matrix, and release minute quantities of bactericidal ionic silver from the surface, into the fluid path.<sup>46</sup> Simulation studies have shown that the total amount of ionic silver eluted into the fluid pathway (with continuous infusion), and infused into the patient, is far less than the level of silver exposure considered to pose a risk to human health.<sup>58,59</sup> Most of the silver absorbed is excreted in feces and urine. Therefore, silver nanoparticle coating might be safely applied, to prevent contamination and the formation of biofilm on the internal surface IVCs. This has great potential to reduce the risk of CRBSI, but has not yet been studied in clinical trials. In 2010, Maki examined the efficiency of a silver nanoparticle-coated connector, compared against non-medicated connectors, in reducing fluid path colonization, by filling these connectors with six bacteria: *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Candida albicans*.<sup>46</sup> After 24 hours and 72 hours of incubation, the remaining viable microorganisms were quantified, and compared with concentrations in control connectors. The biofilm formation of *Enterobacter cloacae* on silver nanoparticle-coated connectors was also examined, concluding that more than 99% of bacteria were killed and biofilm formation was also completely suppressed.<sup>46</sup> However, human bodies are much more complex than the models used in these studies, and large clinical trials are required to assess the clinical efficacy and safety of silver nanoparticle-coated connectors for preventing CRBSIs.

Another advance could be in the use of liposomes, which are artificially prepared vesicles, made of a lipid bilayer, that can be used as drug carriers, especially against colonizing microorganisms. Liposomes can target the matrix (or biofilm) by specific attachment, allowing drugs to be released in the vicinity of the microorganisms (although, in the case of microbial cell adhesion to human cells, there is a need for further knowledge regarding the ability of this system to prevent microbial adhesion but not affect adhered native cells).<sup>60</sup> Therefore, this nanotechnology is a promising research area, but it requires more research to fully understand the mechanism behind the antimicrobial activity. However, several non-clinical studies have been performed on the interaction between liposomes and bacterial biofilms. Halwani et al showed that liposomes were very effective in eradicating antibiotic-resistant *P. aeruginosa* isolates growing in a planktonic or biofilm community.<sup>61</sup> DiTizio et al developed a liposomal hydrogel system that significantly reduced bacterial adhesion to silicone catheters. The system consists of a polyethylene glycol–gelatin hydrogel, in which liposomes containing the antibiotic ciprofloxacin are sequestered.<sup>62</sup> Liposomal antimicrobial lock therapy can potentially be considered as a possible alternative to catheter removal.<sup>63</sup> This technique opens new perspectives for the development of novel antimicrobial catheters.<sup>64</sup>

Polymer drug delivery systems are based on nanocarriers that are formed by mixing polymeric chemical compounds with drugs, to form large and complex molecules that carry the drug across physiological barriers.<sup>65</sup> Polymeric microspheres, polymer micelles, and hydrogel-type materials have been shown to be effective nanocarriers, for enhancing drug targeting specificity, lowering systemic drug toxicity, improving treatment absorption rates, and providing protection for the pharmaceuticals against biochemical degradation.<sup>66</sup> In addition, this system has the possibility to add a pore-forming polymer, which can increase the amount of drug able to be loaded into the carrier.<sup>67</sup> It has been shown that polymeric matrices can be mixed with different antimicrobial agents to prevent bacterial colonization and biofilm formation on medical devices.<sup>65</sup> This system possesses features that are potentially amenable to the manufacture of antimicrobial medical devices, including IVCs.<sup>68</sup> However, in vivo studies are yet to be performed, to test the efficacy of this antibiotic delivery carrier system in reducing bacterial colonization and biofilm formation on catheters.

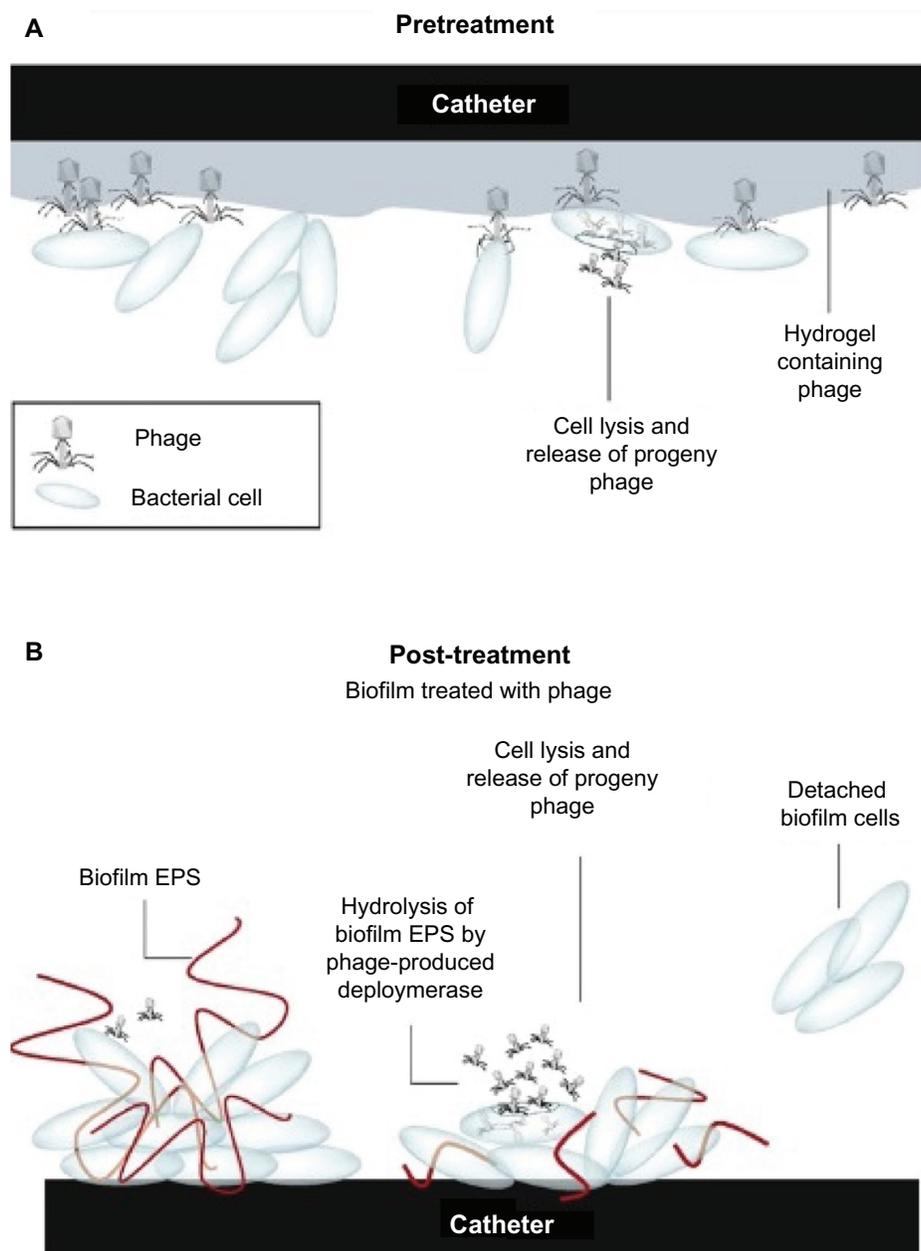
The use of bacteriophages to control CRBSIs caused by biofilms has advantages over treatment with other conventional antimicrobial agents, since phages have very strong

bactericidal activity and can replicate at the site of infection.<sup>69</sup> It was reported that a progeny phage could treat a biofilm formation, due to its ability to propagate radially throughout a biofilm phage, to infect adjacent cells, and degrade the biofilm matrix (Figure 2).<sup>70</sup> In addition, it has been demonstrated that some phages are able to produce enzymes that hydrolyze and degrade the extracellular polymeric matrix of biofilms (Figure 2).<sup>70</sup> A phage active against *S. epidermidis*, incorporated into a hydrogel coating on a catheter, significantly reduced biofilm formation on catheter surfaces.<sup>71</sup> Recently, Fu et al studied the effect (in vitro) of pre-treating hydrogel-coated catheters with *P. aeruginosa* phages, and observed a significant reduction of biofilm formation.<sup>72</sup> This shows that the combination of two nanotechnological approaches can further reduce IVC biofilm formation.<sup>72</sup> However, prior to the use of a phage in humans, there are other aspects to be considered, such as, bacterial resistance to phage, phage inactivation by the human immune system, endotoxins in impure phage, and virulence genes encoded by the phage that can be incorporated into the host bacterial genome.<sup>70</sup> The application of phage mixtures, or engineered phages, might provide better solutions for these problems.

The bioelectric effect is an approach that uses electrical current to prevent biofilm formation and to enhance the activity of antimicrobials against established biofilms.<sup>73</sup> The activity of antimicrobial agents against biofilm microorganisms is enhanced through a relatively weak and continuous electrical current.<sup>73</sup> However, there are few published in vivo studies on using electrical current to prevent medical device-related infection. Del Pozo et al introduced a new concept – the electricidal effect – by demonstrating dose- and time-dependent killing of *S. epidermidis* biofilms after prolonged exposure to low-intensity direct electrical current.<sup>74</sup> The electricidal effect was also tested in vivo, in a rabbit model of *S. epidermidis* chronic foreign body osteomyelitis, which confirmed the bactericidal activity of low amperage electrical current against bacterial biofilms.<sup>75</sup> These results highlight the possibility of applying this therapy to different medical devices, including IVCs.

## Safety and tolerability

The fundamental safety of health care technology is established by the manufacturer, and certified by the relevant national regulatory body for medical drugs and devices (eg, Australian Therapeutic Goods Administration, US Food and Drug Administration, UK Medicines and Healthcare products Regulatory Agency). Efficacy in the clinical setting is tested in trials, as described earlier in this paper. However, the safety



**Figure 2** Mechanisms of hydrogel catheter coated with phage on (A) prevention of bacterial attachment on its surfaces, and (B) treatment of existing biofilm on catheter surfaces.

**Note:** Reprinted from *Trends Microbiol*, 17, Donlan RM, Preventing biofilms of clinically relevant organisms using bacteriophage, 66–72, Copyright (2009), with permission from Elsevier.<sup>70</sup>

**Abbreviation:** EPS, extracellular polymeric substance.

of any device in the clinical setting also relies on adherence to the manufacturer's guidelines, and competency of the end user: the clinician. Sadly, a plethora of research has identified a common, large variability in clinical practice and outcomes, when it comes to IVC insertion and aftercare.<sup>76–80</sup>

Improved patient outcomes for IVC insertion have been associated with dedicated IVC teams, and clinicians with improved skills and increased competencies, as a consequence of effective training and procedural volume.<sup>81–84</sup> In addition, research has demonstrated that clinicians with

minimal experience of inserting central venous catheters have a higher risk of complications arising.<sup>85</sup> Improving and standardizing IVC practices, using multi-modal interventions, has demonstrated a significant reduction in infection rates (2.7 per thousand catheter-days reduced to 0 per thousand catheter-days, at 3 months post-intervention;  $P \leq 0.002$ ) (7.7 per thousand catheter-days reduced to 1.4 per thousand catheter-days, at 18 months post-intervention;  $P \leq 0.002$ ).<sup>27</sup> Furthermore, the results of a prepost study of a post-insertion bundle of evidence-based cares, such as appropriate dress-

ings, suggested a reduction in CRBSI from 5.7 per thousand catheter-days to 1.1 per thousand catheter-days.<sup>28</sup> Another study, on the impact of the introduction of evidence based guidelines on peripheral venous catheter practice, was also associated with a reduction in infection rates, as well as with other improvements, including: completed insertion records (76% vs 58%;  $P < 0.01$ ), correct and sterile fixation localized (92% vs 80%;  $P < 0.05$ ), and catheter complications (4% vs 15%;  $P < 0.01$ ).<sup>86</sup>

The significance of these studies is that they demonstrate the positive impact of evidence-based “best practice” principles and systems, in guiding the insertion and care of IVCs. However, ensuring clinician understanding, acceptance, and adherence to recommended practice is challenging beyond the trial research setting. It involves a careful and strategic combination of staff education and the implementation of systems that promote best practice. Staff need to be educated not only about the clinical problem and related risks, but also about research methodology and levels of evidence. However, in acknowledging the difficulty of achieving adequate compliance levels in practice, and understanding the fallibility of humans, we need to minimize risk and harm through forced decision making systems, or use of technology and equipment that negate clinician choice, and error (eg, central venous catheter insertion trolleys, or pre-filled flush syringes) and protect the patient (eg, impregnated catheters and nanotechnology).

Some clinicians, and even academics, believe that increased use of guidelines or standardized systems reduces and devalues clinical judgment. But, accompanying the freedom of clinical judgments is the risk of inappropriate judgment and error.<sup>87,88</sup> Clinical judgment is not adequately accounted for in a systems analysis approach that may oversimplify health professionals’ choices, and so, within clinical practice, a tradeoff exists between forced choice and free-thinking design.<sup>89</sup>

## Patient-focused perspectives

The financial cost of treating CRBSI is well documented. The US Institute for Healthcare Improvement has quantified the extra cost associated with each CRBSI episode at US\$25,000–\$55,000, which included an extension of the admission by 7 days, on average. The CRBSI-associated mortality rate ranges between 12%–25%.<sup>90</sup> However, the “cost” to patients is less well documented. What is the impact of extended hospital stay (sometimes in isolation), the discomfort associated with local and systemic infection

and related treatment, including ongoing surveillance and laboratory and radiological examinations?

There is a paucity of research describing the impact of CRBSI on the individual patient. Studies that have explored patients’ experiences of being nursed in single room isolation, due to infection while in hospital, have identified adverse effects including boredom, lowered or disturbed mood, and feelings of stigma, along with anxiety about passing the infections to relatives and carers.<sup>91–94</sup> An integrated review of nineteen studies that explored patients’ experiences of infection and/or isolation identified some key common themes. These included a perceived lack of consistent information about the infection, poor understanding of the infection by health care staff, associated fear and stigma, and isolation.<sup>95</sup>

One small, qualitative study explored the patients’ experiences of CRBSI.<sup>96</sup> In this study patients ( $n=18$ ) were somewhat confident about asking staff about health care-associated infection and related infection control issues. But, on the whole, patients were reluctant to question or challenge staff, because they did not want to alienate themselves. Most patients stated that they received little or no information about their infection, until later in their admission, if at all. Patients believed that low staffing levels, the use of temporary (bank) nursing staff, and poor cleanliness were causes of infection. While some patients were resigned to the potential risk of acquiring an infection in hospital, others dreaded it. There was no discussion about how each patient experienced the infection itself, its treatment, and sequelae.

There are few studies also to have examined patient experience of intravenous (IV) therapy or devices. An older paper discussed the potential stress associated with IV therapy, and suggested a number of potential causes, using case studies as references.<sup>97</sup> The author identified three principal sources of anxiety about IV therapy: fear of pain, fear of needles, and fear of confinement. Having identified these factors, the author proposed a range of strategies and approaches for minimizing the stress. These included projection of confidence and competence by the clinician inserting or caring for the IV device, and the use of diversion tactics, for some patients, or detailed explanations of the procedure, equipment, and implications of therapy, for others.

Other research about the patient experience of IV therapy and devices comes from the community setting.<sup>98–101</sup> In a US study conducted using interviews, patients spoke positively about the independence and autonomy that home-based IV therapy afforded them, compared against regular in-hospital treatment. They valued the expertise and support of clinicians associated with the service. But patients also

reflected on the inflexibility of some clinicians and/or guiding protocols, and (sometimes) the use of “blaming or accusatory language” by staff, such as “poor access” or “bad veins”.<sup>100</sup> An Australian study of home-based IV therapy patients echoed similar feelings of independence and liberation in patients who had formerly been required to attend hospital for IV therapy – of experiencing feelings of “getting their life back”. When it is well managed and well supported, infectious outcomes of home-based IV therapy and patient self-management of IVs have been shown to be equivalent to, if not better than, clinician-controlled care. The incidence of catheter-related infections was significantly reduced in the patient education group (2.55 per thousand catheter-days) compared against a control group, with standard care (5.91 per thousand catheter-days) ( $P < 0.01$ ).<sup>101</sup>

The significance of these studies’ results is that they demonstrate patients’ acceptance of, and willingness to embrace, health care technology. Future, trial-based research should incorporate patient evaluation and satisfaction in study protocols.

## Conclusion

Catheter-related infections remain a major problem in health care, being associated with significant morbidity, mortality, and additional medical cost. Microbial biofilm formation makes these infections more complicated, as microbial cells detached from the biofilm can lead to acute infection, and these microorganisms are highly resistant to a large number of antimicrobial agents. New nanotechnologies are being developed in order to overcome problems associated with bacterial or fungal biofilm formation. The nanotechnology approach seems to be one of the most promising research fields for preventing biofilm formation and catheter-related infection, especially against multiresistant strains. However, these will never completely eradicate CRBSI, without additional and ongoing efforts to ensure health professionals consistently adhere to infection prevention measures. In addition, the patient’s experience and acceptance of CRBSI avoidance strategies, including nanotechnologies, must be considered, to maximize the success of such prevention measures.

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The authors declare no conflicts of interest related to this article.

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