Review

CAN ANTIMICROBIAL CENTRAL VENOUS CATHETERS PREVENT ASSOCIATED INFECTION?

Incidence of central venous catheter sepsis
Central venous catheters (CVC) are a major source of sepsis, ranging from local infections at the site of insertion, to septicemia (Maki & Mermel, 1998). The reported incidence of CVC-related infections varies from <1% to 18% (Elliott, 1997) with a frequency of bacteraemia between <1·0 and 13·0 per 1000 catheter days (Bach & Böhrer, 1993; Elliott & Faroqui, 1992). In England and Wales nearly 4000 patients with catheter-related bacteraemias are notified to the Communicable Disease Centre per annum (Elliott, 1993); in the U.S.A. approximately 850,000 catheter-related infections occur annually and of these more than 50,000 are bacteraemias ( Widmer, 1997). Data from the Surveillance and Control of Pathogens of Epidemiological Importance national programme has shown that 70% of all bloodstream infections occurred in patients with CVC ( Centers for Disease Control and Prevention, 1996). A recent approach to prevent CVC-related sepsis (CRS) has been the incorporation or coating of catheter polymers with antimicrobials (Elliott & Faroqui, 1992). A range of these catheters is now commercially available (Table I). In this review the efficacy and role of antimicrobial CVC for the prevention of associated infectious is presented.

Antimicrobial polymers
One of the earliest antimicrobial polymers used for the prevention of infection was gentamicin bound to polymethyl methacrylate (PMMA). This antimicrobial polymer has been incorporated into bone cement or used as beads for the prevention of prosthetic hip infections (Welch, 1978). Dacron with various incorporated antibiotics has also been developed in an attempt to protect vascular grafts from infection. However, to date these have not been widely adopted (Moore et al., 1981; Powell et al., 1983). Polymers bonded with antibiotics have also been produced to provide a prolonged and continuous delivery of prophylactic antimicrobials to prevent CVC infection. Trooskin et al. (1985), for example, used tridecylmethyl-ammonium chloride (TDMAC) to bind penicillin to polyethylene catheter segments. More than 60% of the bound penicillin remained on the catheter surface after 2 weeks in plasma. The potential antimicrobial efficacy of these catheters was confirmed in a rat model challenged with penicillin-sensitive Staphylococcus aureus. Solovsjk et al. (1993) similarly added ampicillin and penicillin which were covalently bound to the polymer. These catheters inhibited the growth of S. aureus in vitro experiments.

Teicoplanin surface coated central venous catheters
Protein deposition onto antimicrobial polymers may reduce their efficacy in vivo. More recent developments have therefore concentrated on surface coating of catheters with antimicrobials rather than chemical bonding. The loosely bound antimicrobials which coat the polymer are relatively easily eluted, which results in antimicrobial activity in the immediate area surrounding the catheter. Romano et al. (1993), for example, challenged a CVC coated with both hydromer and teicoplanin in a mouse model with staphylococci. The antimicrobial coating prevented the formation of abscesses which did occur around uncoated catheters. Jansen et al. (1992a) similarly in vitro demonstrated the protection offered by these teicoplanin-coated catheters when challenged with various microorganisms. The efficacy of teicoplanin in hydromer-coated CVC was further evaluated in a prospective randomized pilot study in patients undergoing major abdominal surgery (Buch et al., 1996). Most of the teicoplanin coating was released during the first 24 h of catheterization, and none was retained after 36 h. No differences were subsequently detected in the degree of bacterial colonization between the teicoplanin-coated and uncoated catheters. Retention of antimicrobial activity was closely linked to protection from infection. These results exemplify the difficulties in retaining antimicrobial activity with compounds not chemically bonded onto polymer surfaces. Slow release of antimicrobials from catheter polymers with activity retained for several weeks should be the aim.

Minocycline–tetracycline-coated central venous catheters
In an in vitro susceptibility study the efficacy of various antimicrobial agents including vancomycin, clindamycin, minocycline, oxacillin and rifampicin when used alone or in combination for the prevention of microbial colonization of catheters has also been studied (Darouiche et al., 1995). The combination of minocycline and rifampicin had antimicrobial activity equivalent to vancomycin and other glycopeptides. Similar in vitro activity was also demonstrated when the inhibitory activity of polyurethane catheters coated with minocycline and rifampicin was compared to catheters coated with other antimicrobial agents (Raad et al., 1995). The inhibitory activity of minocycline- and rifampicin-coated catheters was significantly greater as compared to those coated with vancomycin.

The in vitro efficacy of catheters coated with minocycline and rifampicin has subsequently been determined. In a rabbit model, catheters coated with minocycline and rifampicin were significantly more efficacious than those coated with chlorhexidine gluconate and silver sulphadiazine (CH-SS) in preventing colonization and infection when challenged with
S. aureus (Raad et al., 1996a). The antimicrobials were not permanently bonded to the catheter surface and, following implantation, were released over several weeks. The minocycline and rifampicin catheter (Bio-guard Spectrum™, Cook, Bloomington, Ind., U.S.A.) has been further evaluated in a double-blind randomized clinical trial (Raad et al., 1997). In this study 281 hospitalized patients received either coated antimicrobial catheters (147) or uncoated catheters (151). Microbial colonization occurred in 36 (26%) of uncoated catheters and 11 (8%) of coated catheters (P < 0.001). Catheter-related bloodstream infections developed in seven patients with uncoated catheters and none with coated catheters. Multivariate logistic regression analysis of the results demonstrated that the coated catheter was an independent protective factor against catheter-related colonization. No adverse effects were related to the coated catheters. In a further multi-centre clinical trial (Darouiche et al., 1997, 1999) the minocycline- and rifampicin-coated catheter was compared to CVC coated with CH-SS. A total of 738 evaluable catheters were studied and 356 were impregnated with minocycline and rifampicin and 382 with CH-SS. The CVC impregnated with minocycline and rifampicin were threefold less likely to be colonized and 12-fold less likely to produce catheter-related bloodstream infections than those with CH-SS. The CVC coated with minocycline and rifampicin retained antimicrobial activity for at least 2 weeks (Darouiche et al., 1999; Raad et al., 1998), thereby offering protection from initial colonization and subsequent infection during this period. It is unclear why the catheters impregnated with minocycline and rifampicin compared so favourably with the CH-SS. This may have been due to the minocycline and rifampicin catheter being coated on both the internal and external surfaces whereas the CH-SS is coated only on the external surface. Alternatively minocycline and rifampicin may exhibit enhanced antimicrobial activity as compared to CH-SS, particularly against microorganisms in a biofilm.

**Table I. Antimicrobial catheters available for clinical use.**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Surface coated</th>
<th>Manufacturer or distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline and rifampicin</td>
<td>External and internal</td>
<td>Bio-guard Spectrum™</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cook Spectrum, Cook Critical Care, Bloomington, Ind., U.S.A.</td>
</tr>
<tr>
<td>Chlorhexidine and silver sulphanizine</td>
<td>External</td>
<td>Arrowguard Blue™, Arrow International, Reading, Pa., U.S.A.</td>
</tr>
<tr>
<td>Silver and platinum particles in a carbon-based polyurethane*</td>
<td>External and internal</td>
<td>Vygon (UK) Ltd, Gloucester, U.K.</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>External and internal</td>
<td>Becton Dickinson (UK) Ltd, Swindon, U.K.</td>
</tr>
<tr>
<td>BZC-heparin bonded</td>
<td>External and internal</td>
<td>AMC Thromboshield™, Baxter, Irvine, Calif., U.S.A.</td>
</tr>
</tbody>
</table>

*Only available as a PICC (peripherally inserted central catheter).

Cefazolin-bonded central venous catheters

Cefazolin bonded onto CVC with a cationic surfactant has also been evaluated (Kamal et al., 1991) on surgical intensive care (ICU) patients. A significant reduction in the number of infections associated with this cephalosporin-coated CVC as compared to uncoated catheters was reported (2% v 14%). In a more extensive study, also on ICU patients, cefazolin-coated catheters were compared to a standard non-antimicrobial catheter. The antibiotic-coated CVC resulted in a significant reduction in catheter-associated bacteraemia and the cumulative risk of infection was significantly reduced (Kamal et al., 1998). Other β-lactam antibiotics have also been used to coat catheters, including dicloxacillin (Sheretz et al., 1989) which reduced colonization and catheter infections in a mouse model.

Antiseptic-coated catheters

Concern has been raised about the possible emergence of antimicrobial resistance with the widespread use of antibiotics in catheter materials. Antibiotic combinations such as minocycline and rifampicin used to prevent catheter-related sepsis may, however, reduce the likelihood of the emergence of resistance (Yoursassowsky et al., 1981; Darouiche et al., 1991). The protective action of minocycline has been related to its lipophilic nature and ability to penetrate into tissues and biofilms accessed by rifampicin. However, as has been shown with many topically applied antimicrobials, emergence of resistance may be stimulated by the use of catheters, particularly those coated with only a single antibiotic. Research to reduce catheter-related sepsis has therefore also been focused on the application of antiseptics rather than antimicrobials. The more recent emergence of vancomycin-resistant *Staphylococcus aureus* in both Japan and the United States has highlighted the need to restrict the use of antibiotics such as the glycopeptides (Smith et al., 1999), and the use of antiseptic coated catheters may facilitate such an
approach. In an early study Irgasan® (Ciba-Geigy, U.K.) was incorporated into plastic made of ethylvinyl acetate (EVA), polyethylene or polypropylene. It was shown that Irgasan inhibited a wide range of microorganisms (Kingston et al. 1986). When polymers containing this antimicrobial were challenged with S. aureus in a rabbit model, protection from colonization and subsequent infection was demonstrated. However, the Irgasan was eluted relatively rapidly, resulting in only short-term antimicrobial protection (Kingston et al. 1992). Another antiseptic-containing polymer which has been developed is iodine complexed with polyvinylpyrrolidone (Jansen et al. 1992b). When challenged with microorganisms, colonization was inhibited by the iodine-complexed polymers (Jansen et al. 1992b). However, these antiseptic catheters remain to be clinically evaluated.

Chlorhexidine–silver-sulphadiazine-coated central venous catheters

The use of CH-SS, referred to earlier in comparative studies, has been extensively studied. These catheters are coated only on the external surface and the antimicrobials are released slowly over at least 15 d (Arrowguard Blue®, Arrow International Inc., Reading Pa., U.S.A.). A synergistic effect of chlorhexidine gluconate and silver sulphadiazine was demonstrated by Modak & Sampath (1992). The chlorhexidine affects the bacterial cytoplasmic membrane and enables uptake of silver ions by the cell. The silver binds to the bacterial DNA and inhibits replication. In a clinical investigation on 40 post-operative cardiac surgical patients a significant reduction in the incidence of microbial colonization of catheter distal tips with the CH-SS-bonded catheters was recorded (Bach et al. 1993). Clemence et al. (1993) also demonstrated a reduction in catheter-related septicemia with these catheters in a crossover study of patients being treated on intensive care units; there was a 60% reduction in the rate of bacteremias. Maki et al. (1997) have also carried out a large comparative clinical study with the CH-SS catheters as compared to control non-antimicrobial devices. The presence of the antimicrobial significantly decreased the number of colonized catheters and PVC-related bacteremias in ICU patients. Conversely, Logghe et al. (1997) have reported that the CH-SS catheters in patients with various underlying haematological malignancies did not reduce the risk of bacteremias or septicemias. In a further clinical study Heard et al. (1998) demonstrated a decrease in bacterial growth on the CH-SS catheters, but there was no significant effect on the incidence of catheter-related bacteremias. Two further studies have also not shown a protective effect of the CH-SS catheter against infection (Pemberton et al. 1996; Criesi et al. 1996). The disparity in the results may be due to several factors including differences in the types of patients studied, the skin preparations used, post-operative wound care, and bandages selected. In Maki et al. (1997) the patients had an average duration of catheterization of only 6 d. In comparison, in the study by Logghe et al. (1997) the average time of catheterization was 20 d and the catheter-related infections did not occur until the CVC had been in place for ≥5 d. The increased loss of CH-SS by elution during the 20 d as compared to the 6 d therefore offers a further possible explanation for the reduced efficacy noted by Logghe et al. (1997). Further studies are required to evaluate the role of CH-SS in preventing CVC infection, particularly in patients with catheters in situ for >6 d.

Hypersensitive reactions occasionally occur when patients are exposed to chlorhexidine or silver sulphadiazine. The possibility that such reactions may occur through the use of a catheter with a relatively small amount of CH-SS is unlikely. In clinical trials of CH-SS catheters, and from extensive use in the United States, this has been borne out. However, anaphylactic reactions have been reported with chlorhexidine (Ohtoshi et al. 1986; Cheung & O’Leary, 1985), and more recently with CH-SS-coated catheters in Japan (World Health Organization, 1997). Possible explanations for these reactions include genetic predisposition or previous exposure to chlorhexidine-containing products, resulting in increased sensitivity. Awareness of this, albeit rare, side-effect is important.

A CVC coated with metallic silver (Pellethane®, Fresenius AG, Germany) has also been developed. This anti-infective polyurethane catheter prevented microbial colonization of the device in in vitro tests (Jansen et al. 1994) and in oncology patients (Goldschmidt et al. 1995). There was a significant reduction in catheter-related infections. These catheters do not contain chlorhexidine, reducing the likelihood of anaphylactic reactions. This catheter, however, awaits further clinical evaluation.

Benzalkonium-chloride-coated central venous catheters

The hub, the distal tip of the catheter on insertion via the skin (Elliott et al. 1997), the internal lumen and external surface of a catheter are primary sources of microorganisms causing colonization and infection (Sitges-Serra et al. 1984; Linares et al. 1985; Tebbs et al. 1995). Coating both catheter surfaces is therefore important for the prevention of CVC infection as exhibited by the minocycline and rifampicin catheter evaluations. More recently a triple lumen polyurethane catheter coated with hydromer and benzalkonium chloride (BZC) has been developed. Unlike the CH-SS catheter, the BZC catheter is coated on both the internal and external surfaces (Becton Dickinson Ltd, Swindon). Benzalkonium chloride is a quaternary ammonium compound which inhibits microbial membrane activity and DNA replication (Elliott & Tebbs, 1993). In an in vitro assessment of this antimicrobial catheter, microbial colonization was significantly reduced both on the internal and external surfaces when challenged by a wide range of microorganisms (Elliott & Tebbs, 1993, 1998; Tebbs & Elliott, 1994). Microbial colonization is considered to be a prerequisite of infection, and these findings suggest that the BZC-coated catheter may offer protection from subsequent infection on both surfaces of the device. In a clinical trial comparing the BZC catheter with a non-antimicrobial device, reduced colonization was demonstrated (Elliott & Farquhi, 1992; Elliott et al. 1998). The use of the catheter has not been associated with any adverse effects in 150 patients studied to date. This is consistent with the wide applications of BZC in medicine, in particular as a preservative, where it is well tolerated. The BZC catheter should be distinguished from BZC-heparin.
bonded catheters (AMC Thromboshield™, Baxter, Irvine, Calif., U.S.A.) (Mermel et al. 1993) in which the antimicrobial is bound to heparin, unlike the device studied by Elliott et al. (1998) which is coated unbound. The anti-infective component of the RZC-heparin-bound-catheter, which is also applied to both the external and internal surfaces, has been shown in rat models to offer limited long-term protection from microbial colonization (Sampath et al. 1995). The presence of heparin to reduce thrombus formation on this catheter may further reduce microbial colonization. However, full clinical evaluation is awaited on this device.

Other antimicrobial active polymers

Low amperage electrical current applied to carbon-impregnated catheter has also been developed to prevent CVC-related sepsis. In in vitro studies the electrical negatively charged catheter repelled microbialisms when current was applied at levels which are cardiovascularly safe (Elliott et al. 1990; Liu et al. 1993). The bactericidal activity of the low amperage current resulted from hydrogen peroxide and free chlorine produced by electrolysis at the catheter surface (Liu et al. 1997). Raad et al (1996b) have also demonstrated in an in vitro study that silver iontophoretic catheters, when challenged with S. aureus, prevented colonization. It is claimed that electrolytes in body fluids interact with the silver and platinum particles in the polymer resulting in release of silver ions. This technology, which has been applied to a peripherally implanted central catheter (Olimpicc™, Vygon (UK) Ltd) awaits clinical evaluation. Costerton et al (1994), have also shown enhancement of the bactericidal activity of antibiotics against biofilm embedded bacteria by the use of an electric field. The application of low amperage electrical current, perhaps in combination with antimicrobials, may provide a novel method for prostheses to be protected from microbial colonization and subsequent sepsis. Further developments of the application of electricity are awaited.

Clinical application of antimicrobial catheters

Several antimicrobial catheters appear, from the available clinical data, to reduce the incidence of microbial colonization and infections associated with CVC. The increasing number of multiple antibiotic resistant bacteria and fungi may, however, limit the use of antibiotics incorporated into CVC. In comparison, the widespread emergence of antibiotic-resistant microorganisms is less likely to occur, because their action is via basic chemical reactions, unlike antibiotics which are generally under genetic and hence mutable and transmissible control (Russell et al. 1986; Ascenzi, 1996). Low-level plasmid-mediated resistance to cationic biocides such as chlorhexidine and quaternary ammonium compounds has, however, been reported in antibiotic-resistant strains of staphylococci (Leehporn et al. 1994). A link between antibiotic and biocide resistance has also been highlighted (Russell et al. 1998) and this should be taken into account in the selection and application of antimicrobials used in catheters.

Antiseptic-impregnated CVC also appear to offer a cost benefit (Civetta, 1996). The cost of treating a patient with CVC sepsis, not requiring ITU treatment, is nearly £2000 in the U.K. (Moss & Elliott, 1997). Raad et al (1997), in a study on ITU patients with CVC sepsis, further demonstrated potential hospital savings of $500 000 per annum in a U.S. teaching hospital. However, more studies are required to fully evaluate the cost benefit of these devices. The current data on efficacy of these antimicrobial CVC is also still limited, with some unexplained differences in findings. These differences most likely reflect the multitude of factors which can influence the risk of CRS, including catheter care, insertion protocols and antiseptic policies. Even the results of the extensive well-controlled trials such as those by Maki et al (1997) and Raad et al (1997) are difficult to translate to other clinical situations (Pearson & Abrutyn, 1997). These two studies were carried out in teaching hospitals which had relatively high rates of CRS as compared to other published levels (Centers for Disease Control and Surveillance, 1996). The efficacy and value of antimicrobial catheters in units with lower rates of sepsis is therefore unclear.

In which clinical scenarios should these antimicrobial catheters therefore be used? The currently available antimicrobial catheters offer protection from infection for only approximately 2 weeks. Their clinical use is therefore limited to situations where short-term CVC are required, including stem cell transplantation, replacement for failed Hickman line insertions, and for acute septic episodes. It is important that existing recommendations for good practice are implemented and audited (Elliott et al. 1994), with appropriate aseptic techniques (Mass et al. 1998). For example, the correct choice and use of cutaneous antiseptics is essential as these can influence the subsequent incidence of infection. The use of chlorhexidine rather than povidone–iodine for skin disinfection prior to insertion of an intravascular device and post-insertion site care can reduce the incidence of intravascular catheter-related sepsis (Maki & Mermel, 1998; Garland et al, 1995; Mimoz et al, 1996). Other facts of catheter care which should be considered include choice of appropriate dressings and the aseptic techniques used when connectors are opened. New techniques associated with the use of catheters, for example the application of needleless connectors (Brown et al, 1997), should always be fully evaluated before use on patients. Antimicrobial catheters should be considered as an addition to these approaches rather than attempting to overcome poor practice with a related high incidence of CRS. The antimicrobial catheters should be reserved, until more data becomes available, for high-risk patients such as those on intensive care units with short-term catheters, particularly in situations where the background rates of CRS are high. In clinical situations where the CRS is already low, or when the catheters are being used for patients undergoing long-duration treatment, for example in haematological malignancy, a reduction of the incidence of bacteraemia may not ensue from the use of currently available antimicrobial catheters including the CH-SS (D’Hoore, 1998). If antimicrobial catheters are not used selectively the advantages offered by them may be negated by the further emergence of microbial resistance and the escalating costs of these infections will continue (Moss & Elliott, 1997).
ACKNOWLEDGMENTS

I thank Mary McDermott for skilful secretarial support, and Dr Peter Lambert and Mrs Helen Moss for useful comments.

Department of Clinical Microbiology, T. S. J. Elliott
Queen Elizabeth Hospital, Birmingham

REFERENCES


Jansen, B., Jansen, S., Peters, G. & Pulverer, G. (1992a) In-vitro efficacy of a central venous catheter (‘Hydrocath’) loaded with...


**Keywords:** antimicrobial, antiseptic, central venous catheters.