British Journal of Haematology, 1999, **107**, 235–241

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 septicaemia (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 infections 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 tridodecylmethyl-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*. Solovskj *et al* (1993) similarly added ampicillin and penicillin which were covalently bound to the polymer. These catheters inhibited the growth of *S. aureus* in *in vitro* experiments.

Correspondence: Dr T. S. J. Elliott, Department of Clinical Microbiology, Queen Elizabeth Hospital, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH.

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 (Bach *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 vivo* 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

Table I. Antimicrobial catheters available for clinical use.

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

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

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 ($P<0{\cdot}001$). 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.

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 (Yourassowsky *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 septicaemia with these catheters in a crossover study of patients being treated on intensive care units; there was a 60% reduction in the rate of bacteraemias. 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 CVC-related bacteraemias 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 bacteraemias or septicaemias. 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 bacteraemias. 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 $\geqslant$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 & Faroqui, 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 BZC-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 catheters has also been developed to prevent CVC-related sepsis. In *in vitro* studies the electrical negatively charged catheters repelled microorganisms 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 antiseptic-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 (Leelnporn *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, Queen Elizabeth Hospital, Birmingham

T. S. J. Elliott

REFERENCES

Ascenzi, J.M. (1996) Antiseptics and their role in infection control. In *Handbook of Disinfectants and Antiseptics* (ed. by J. M. Ascenzi), Chapter 4. Marcel Dekker, New York.

Bach, A. & Böhrer, H. (1993) Infektionen durch intravasal Katheter. *Anästhesiologie und Intensivmediv Notfallmedizin Schmerztherapie*, **28,** 404–414.

Bach, A., Darby, D., Böttiger, B., Böhrer, H., Motsch, J. & Martin, E. (1996) Retention of the antibiotic teicoplanin on a hydromer-coated central venous catheter to prevent bacterial colonization in postoperative surgical patients. *Intensive Care Medicine*, **22,** 1066–1069.

Bach, A., Geiss, M., Geiss, H.K. & Sonntag, H.G. (1993) Prevention of catheter-related colonization by silver-sulfadiazine-chlorhexidine (SSC) bonding: results of a pilot study in critical care patients. *Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Chemotherapy, New Orleans, LA, 1993*. Abstract 1621, p. 415. American Society for Microbiology, Washington, D.C.

Brown, J.D., Moss, H.A. & Elliott, T.S.J. (1997) The potential for catheter microbial contamination from a needleless connector. *Journal of Hospital Infection*, **36,** 181–189.

Centers for Disease Control and Prevention (1996) National Nosocomial Infection Surveillance System Semiannual Report, December 1996. Centers for Disease Control and Prevention, Atlanta, Ga.

Cheung, J. & O'Leary, J.J. (1985) Allergic reaction to chlorhexidine in an anethetized patient. *Anaesthetic Intensive Care*, **13,** 429.

Civetta, J.M. (1996) Antiseptic-impregnated non-tunneled central venous catheters: reducing infection risks and associated costs. *Dialysis and Transplantation*, **25,** 784–798.

Clemence, M.A., Jernigan, J.A., Titus, M.A., Duani, D.K. & Farr, B.M. (1993) A study of an antiseptic impregnated central venous catheter for prevention of bloodstream infections. *Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, 1993*. Abstract 1624, p. 416. American Society for Microbiology, Washington, D.C.

Costerton, J.W., Ellis, B., Lam, K., Johnson, F. & Khoury, A.E. (1994) Mechanism of electrical enhancement of efficacy of antibiotics in killing biofilm bacteria. *Antimicrobial Agents and Chemotherapy*, **38,** 2803–2809.

Criesi, D.L., Albrecht, R.M., Volkers, P.A. & Scholten, D.J. (1996) Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. *American Surgeon*, **62,** 641–646.

Darouiche, O., Raad, I.I., Bodey, G.P. & Musher, D.M. (1995) Antibiotic susceptibility of staphylococcal isolates from patients with vascular catheter-related bacteria: potential role of the combination of minocycline and rifampicin. *International Journal of Antimicrobial Agents*, **6,** 31–36.

Darouiche, R., Wright, C., Hamill, R., Koza, M., Lewis, D. & Markowski, J. (1991) Eradication of colonization by methicillin-resistant *Staphylococcus aureus* by using oral minocycline-rifampin and topical mupirocin. *Antimicrobial Agents and Chemotherapy*, **35,** 1612–1615.

Darouiche, R., Raad, I., Heard, S., Rand, K., Khardori, N., Harris, R., Wenker, O. & Mayhall, G. (1997) A prospective, randomized, multicenter clinical trial comparing central venous catheters impregnated with minocycline and rifampin vs. chlorhexidine gluconate and silver sulfadiazine. *37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, 1997*. Abstract LB-22.

Darouriche, R.O., Raad, I.I., Heard, S.O., Thornby, J.I., Wenker, O.C., Gabrielli, A., Berg, J., Khardori, N., Hanna, H., Hachem, R., Harris, R.L. & Mayhall, G. (1999) A comparison of two antimicrobial-impregnated central venous catheters. *New England Journal of Medicine*, **340,** 1–8.

D'Hoore, W. (1998) A meta-analysis dealing with the effectiveness of chlorhexidine and silver-sulfadiazine impregnated central venous catheters. *Journal of Hospital Infection*, **40,** 166–168.

Elliott, T.S.J. (1993) Line-associated bacteraemias. *Communicable Disease Report*, **3,** R23–R24. Public Health Laboratory Services, Colindale, London.

Elliott, T.S.J. (1997) Catheter-associated infections: new developments in prevention. *Current Topics in Intensive Care* (ed. by H. Burchard), pp. 182–205. Saunders, London.

Elliott, T.S.J. & Faroqui, M.H. (1992) Infections and intravascular devices. *British Journal of Hospital Medicine*, **48,** 496–503.

Elliott, T.S.J., Faroqui, M.H., Armstrong, R.F. & Hanson, G.C. (1994) Infection control in practice: guidelines for good practice in central venous catheterisation. *Journal of Hospital Infection*, **28,** 163–176.

Elliott, T.S.J., Holford, J., Sisson, P. & Byrne, P. (1990) A novel method to prevent catheter-associated infections. *Journal of Medical Microbiology*, **33,** 2.

Elliott, T.S.J., Moss, H.A., Tebbs, S.E., Herbst, T., Isaac, J., Brown, J.D. & Faroqui, M.H. (1998) A new antimicrobial central venous catheter for the prevention of infections. *Abstracts of the 4th International Conference of the Hospital Infection Society, Edinburgh, 13–17 September 1998*, P.8.1.1.

Elliott, T.S.J., Moss, H.A., Tebbs, S.E., Wilson, I.C., Bonser, R.S., Graham, T.R., Burke, L.P. & Faroqui, M.H. (1997) A novel approach to investigate the source of microbial contamination of central venous catheters. *European Journal of Clinical Microbiology*, **16,** 210–213.

Elliott, T.S.J. & Tebbs, S.E. (1993) Intravascular catheters impregnated with benzalkonium chloride. *Journal of Antimicrobial Chemotherapy*, **32,** 905–906.

Elliott, T.S.J. & Tebbs, S.E. (1998) Prevention of central venous catheter-related infection. *Journal of Hospital Infection*, **40,** 193–201.

Garland, J.S., Buck, R.K., Maloney, P., Durkin, M.N., Toth-Lloyd, S., Duffy, M., Szocik, P., McAuliffe, T.L. & Goldman, D. (1995) Comparison of 10% povidone-iodine and 0·5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial. *Pediatric Infectious Diseases Journal*, **15,** 510–516.

Goldschmidt, H., Hahn, U., Salwender, H-J., Haas, R., Jansen, B., Wolbring, P., Rinck, M. & Hunstein, W. (1995) Prevention of catheter-related infections by silver coated central venous catheters in oncological patients. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene*, **283,** 215–223.

Heard, S.O., Wagle, M., Vijayakumar, E., McLean, S., Brueggeman, A., Naplitano, L.M., Edwards, L.P., O'Connell, F.M., Puyana, J.C. & Doern, G.V. (1998) Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. *Archives of Internal Medicine*, **158,** 81–87.

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

teicoplanin to prevent bacterial colonization. *Journal of Hospital Infection*, **22,** 93–107.

Jansen, B., Kristinsson, K.G., Jansen, S., Peters, G. & Pulverer, G. (1992b) In-vitro efficacy of a central venous catheter complexed with iodine to prevent bacterial colonization. *Journal of Antimicrobial Chemotherapy,* **30,** 135–139.

Jansen, B., Rinck, M., Wolbring, P., Strohmeier, A. & Jahns, T. (1994) *In vitro* evaluation of the antimicrobial efficacy and biocompatibility of a silver-coated central venous catheter. *Journal of Biomaterial Applications*, **9,** 55–70.

Kamal, G.D., Divishek, D., Kumar, G.C., Porter, B.R., Tatman, D.J. & Adams, J.R. (1998) Reduced intravascular catheter-related infection by routine use of antibiotic-bonded catheters in a surgical intensive care unit. *Diagnostic Microbiology and Infectious Disease*, **30,** 145–152.

Kamal, G.D., Ptaller, M.A., Rempe, L.E. & Jebson, P.J.R. (1991) Reduced intravascular catheter infection by antibiotic bonding. *Journal of the American Medical Association*, **265,** 2364–2368.

Kingston, D., Birnie, E.D.C., Martin, J., Pearce, P.C., Menek, S. & Quinn, C.M. (1992) Experimental pathology of intravenous polyurethane cannulae containing disinfectant. *Journal of Hospital Infection*, **20,** 257–270.

Kingston, D., Seal, D.V. & Hill, I.D. (1986) Self-disinfecting plastics for intravenous catheters and prosthetic inserts. *Journal of Hygiene, Cambridge*, **96,** 185–198.

Leelnporn, A., Paulsen, I.T., Tennent, J.M., Littlejohn, T.G. & Skurray, R.A. (1994) Multidrug resistance to antiseptics and disinfectants in coagulase-negative staphylococci. *Journal of Medical Microbiology,* **40,** 214–220.

Linares, J., Sitges-Serra, A., Garau, J., Perez, J.L. & Martin, R. (1985) Pathogenesis of catheter sepsis: a prospective study with quantitative and semi-quantitative cultures of catheter hub and segments. *Journal of Clinical Microbiology,* **21,** 357–360.

Liu, W-K., Brown, M.W.R. & Elliott, T.S.J. (1997) Mechanisms of the bacterial activity of low amperage electric current (DC). *Journal of Antimicrobial Chemotherapy,* **39,** 687–695.

Liu, W-K., Tebbs, S.E., Byrne, P.O. & Elliott, T.S.J. (1993) The effects of electric current on bacteria colonising intravenous catheters. *Journal of Infection*, **27,** 261–269.

Logghe, C., Van Ossel, C., D'Hoore, W., Ezzedine, H., Wauters, G. & Haxhe, J.J. (1997) Evaluation of chlorhexidine and silver-sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukaemic patients: a randomized controlled trial. *Journal of Hospital Infection*, **37,** 145–156.

Maki, D.G. & Mermel, L.A. (1998) Infections due to infusion therapy. *Hospital Infections*, 4th edn (ed. by J. V. Bennett and P. S. Brachman), p. 689. Lippincott-Raven Publishers, Philadelphia.

Maki, D.G., Stolz, S.M., Wheeler, S. & Mermel, L.A. (1997) Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. *Annals of Internal Medicine,* **127,** 257–266.

Mass, A., Flament, P., Pardou, A., Deplano, A., Dramaix, M. & Struelens, M.J. (1998) Central venous catheter-related bacteraemia in critically ill neonates: risk factors and impact of a prevention programme. *Journal of Hospital Infection*, **40,** 211–224.

Mermel, L.A., Stolz, S.M. & Maki, D.G. (1993) Surface antimicrobial activity of heparin-bonded and antiseptic-impregnated vascular catheters. *Journal of Infectious Diseases*, **167,** 920–924.

Mimoz, O., Pieroni, L., Lawrence, C., Edouard, A., Costa, Y., Samii, K. & Brun-Buisson, C. (1996) Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Critical Care Medicine,* **24,** 18818–1823.

Modak, S.M. & Sampath, L. (1992) Development and evaluation of a new polyurethane central venous antiseptic catheter: reducing central venous catheter infections. *Infections in Medicine*, **June,** 23–29.

Moore, W.A., Chapril, M., Seiffert, G. & Keown, K. (1981) Development of an infection-resistant vascular prosthesis. *Archives of Surgery,* **116,** 1403.

Moss, H.A. & Elliott, T.S.J. (1997) The cost of infection related to central venous catheters designed for long-term use. *British Journal of Medical Economics*, **11,** 1–7.

Ohtoshi, Y., Yamauchi, N., Tadokoro, K., Miyachi, S., Suzuki, S., Miyamoto, T. & Muranka, M. (1986) IgE antibody-mediated shock reaction caused by topical application of chlorhexidine. *Clinical Allergy,* **16,** 155–161.

Pearson, M.L. & Abrutyn, E. (1997) Reducing the risk for catheter-related infections: a new strategy. *Annals of Internal Medicine*, **127,** 304–306.

Pemberton, L.B., Ross, V., Cuddy, P., Kremer, H., Fessler, T. & McGurk, E. (1996) No difference in catheter sepsis between standard and antiseptic central venous catheters. *Archives of Surgery,* **131,** 986–989.

Powell, T.W., Bernham, S.J. & Johnson, G. (1983) A passive system using rifampicin to create an infection-resistant vascular prosthesis. *Surgery,* **945,** 765–769.

Raad, I., Darouiche, R., Dupuis, J., Abi-Said, D., Gabrielli, A., Hachem, R., Wall, M., Harris, R., Jones, J., Buzaid, A., Robertson, C., Shenaq, S., Curling, P., Burke, T., Ericsson, C., and the Texas Medical Center Catheter Study Group (1997) Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. *Annals of Internal Medicine*, **127,** 267–274.

Raad, I., Darouiche, R., Hachem, R., Mansouri, M. & Bodey, G.P. (1996a) The broad-spectrum activity and efficacy of catheters coated with minocycline and rifampin. *Journal of Infectious Diseases*, **173,** 418–424.

Raad, I., Darouiche, R., Hachem, R., Sacilowski, M. & Bodey, G.P. (1995) Antibiotics and prevention of microbial colonization of catheters. *Antimicrobial Agents and Chemotherapy,* **39,** 2397–2400.

Raad, I., Hachem, R. & Zermeno, A. (1996b) Silver iontophoretic catheter: a prototype of a long-term antiinfective vascular access device. *Journal of Infectious Diseases*, **173,** 495–498.

Raad, I.I., Darouiche, R.O., Hachem, R., Abi-Said, D., Safar, H., Darnule, T., Mansouri, M. & Morck, D. (1998) Antimicrobial durability and rare ultrastructural colonization of indwelling central catheters coated with minocycline and rifampin. *Critical Care Medicine,* **26,** 219–224.

Romano, G., Berti, M., Goldstein, B.P. & Borghi, A. (1993) Efficacy of a central venous catheter (Hydrocath®) loaded with teicoplanin in preventing subcutaneous staphylococcal infection in the mouse. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene*, **279,** 426–433.

Russell, A.D., Hammond, S.A. & Morgan, J.R. (1986) Bacterial resistance to antiseptics and disinfectants. *Journal of Hospital Infection,* **7,** 213–225.

Russell, A.D., Tattawasart, U., Maillard, J-Y. & Furr, J.R. (1998) Possible link between bacterial resistance and use of antibiotics and brocides. *Antimicrobial Agents and Chemotherapy,* **42,** 2151.

Sampath, L.A., Chowdhury, N., Caraos, L. & Modak, S.M. (1995) Infection resistance of surface modified catheter with either short-lived or prolonged activity. *Journal of Hospital Infection*, **30,** 201–210.

Sherertz, R.J., Forman, D.M. & Solomon, D.D. (1989) Efficacy

of dicloxacillin-coated polyurethane catheters in preventing subcutaneous *Staphylococcus aureus* infection in mice. *Antimicrobial Agents and Chemotherapy*, **33,** 1174–1178.

Sitges-Serra, A., Puig, P., Linares, J., Perez, J.L., Farrrero, N., Jaurrieta, E. & Garam, J. (1984) Hub colonisation as the initial step in an outbreak of catheter-related sepsis due to coagulase-negative staphylococci during parenteral nutrition. *Journal of Parenteral Nutrition*, **8,** 668–672.

Smith, T.L., Pearson, M.L., Wilcox, K.R., Cruz, C., Lancaster, M.V., Robinson-Dunn, B., Tenover, F.C., Zervos, M.J., Band, J.D., White, E. & Jarvis, E.R. (1999) Emergence of vancomycin resistance in *Staphylococcus aureus*. *New England Journal of Medicine*, **340,** 493–500.

Solovskj, M.V., Ulbrich, K. & Kopecek, J. (1993) Synthesis of N-(2-hyroxypropyl)methacrylamide copolymers with antimicrobial activity. *Biomaterials*, **4,** 44–48.

Tebbs, S.E. & Elliott, T.S.J. (1994) Modification of central venous catheter polymers to prevent *in vitro* microbial colonisation. *European Journal of Clinical Microbiology and Infectious Diseases*, **13,** 111–117.

Tebbs, S.E., Trend, V. & Elliott, T.S.J. (1995) The potential reduction of microbial contamination of central venous catheters. *Journal of Infection*, **30,** 107–113.

Trooskin, S.Z., Donetz, A.P., Harvey, R.A. & Greco, R.S. (1985) Prevention of catheter sepsis by antibiotic bonding. *Surgery*, **97,** 547–551.

Welch, A.G. (1978) Antibiotics in acrylic bone cement. *Journal of Biomedical Material Research*, **12,** 679–700.

Widmer, A.F. (1997) Central venous catheters. *Catheter-Related Infections* (ed. by H. Seifert, B. Jansen and B. M. Farr), pp. 183–215. Marcel Dekker, New York.

World Health Organization (1997) Central venous catheters (Arrowguard®) recalled: anaphylactic shock. Information Exchange System, Alert No. 62, 15 September 1997.

Yourassowsky, E., Van der Linden, M.P., Lismont, M.J. & Crokaert, F. (1981) Combination of minocycline and rifampin against methicillin- and gentamcin-resistant *Staphylococcus aureus*. *Journal of Clinical Pathology*, **34,** 559–563.

Keywords: antimicrobial, antiseptic, central venous catheters.