THE SOURCE, COST AND PREVENTION OF
CENTRAL VENOUS CATHETER-RELATED INFECTION

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SUMMARY

Central venous catheters have become an integral part of patient management however they are associated with many complications including infection. Despite efforts being made to reduce the incidence of such infections the problem continues to increase and has resource implications for the Health Service. Studies relating to the source of microorganisms causing CVC-associated infection, the cost of such infections and the efficacy of an antimicrobial catheter have been undertaken. Thirty patients who required a CVC as part of their medical management and underwent cardiac surgery had the distal tips of their catheters sampled whilst *in situ*. Sampling took place within 1 h of catheter placement. Bacteria were isolated from 16% of the catheter distal tips sampled *in situ*. The guidewires used to insert the devices were also contaminated (50%). When CVC were inserted *via* a protective sheath, avoiding contact with the skin, the incidence of microbial contamination was reduced. These findings suggest that despite rigorous skin disinfection and strict aseptic technique, viable microorganisms are impacted onto the distal tip of CVC during the insertion procedure. Needleless intravascular access devices have been introduced in order to reduce the incidence of needlestick injury. However, it was unclear whether such connectors would act as a portal of entry for microorganisms to CVC. The efficacy of these devices was investigated. Within the controlled laboratory environment it was demonstrated that needleless devices, when challenged with microorganisms, did not allow the passage of microbes when fluid was injected. This therefore suggested that the devices should not increase the risk of catheter colonisation. When used in clinical practice however, microbial contamination of the needleless connectors was 55 %, in comparison to the routinely used luer connectors (23%). The cost of infections associated with CVC was determined. Twenty patients catheterised with a CVC designed for long term use who were admitted to hospital with a presumptive diagnosis of catheter-related infection were studied. The treatment given specifically for this infection was costed. The mean cost of such an infection was £1781.81. Throughout the UK this may amount to £2,565,906 per annum. The cost of infections associated with CVC designed for short term use was estimated to be between 5 and 7 million pounds per annum in the UK. In an attempt to reduce both the incidence and cost of catheter-related infection antimicrobial CVC have been developed. The efficacy of a novel polyurethane CVC impregnated on both the internal and external catheter surface with the quaternary ammonium compound benzalkonium chloride was investigated. Eighty eight patients received an antimicrobial catheter and 78 patients a conventional polyurethane CVC. The antimicrobial CVC resulted in a reduction in microbial colonisation of the external and internal polymer surfaces as compared to the control device. The observed reduction in microbial colonisation with the antimicrobial CVC may decrease the likelihood of subsequent infection, offering a useful approach to the prevention of catheter-related infections.

Key Words: Needleless connector, antimicrobial, benzalkonium chloride

DEDICATION

To Mum and Dad

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1. Introduction

Synthetic intravascular (IV) catheters were introduced for hospital use in the 1940's (Meyers, 1945) and have since been developed to form an essential part of patient management. Intravascular devices are used for the administration of drugs, fluid replacement and parenteral nutrition as well as providing the means to monitor a patient's haemodynamic state. Haemodynamic monitoring is carried out with central venous catheters (CVC), arterial cannulae and pulmonary artery catheters (Swan-Ganz). Although many IV devices are used widely throughout the world they are still associated with many complications (Table 1-1).

First reports of infections associated with IV devices appeared in 1947 when Neuhof and Seley noted six cases of sepsis attributed to venous cannulation. Throughout the 1950's further reports of complications were documented (Moncrief, 1958., Phillips and Eyre, 1958., Indar, 1959), ranging from inflammation at the site of insertion to life threatening septicaemia. Catheter-related sepsis (CRS) remains a significant clinical problem, having a recognised associated morbidity and mortality (Maki, 1994., Pittet *et al.* 1994). Many factors including the patient, medical personnel and the design of the device influence the subsequent development of CRS (section 1.5). The reported incidence of infective complications associated with IV catheters varies according to the device used. Maki *et al.* (1973) demonstrated that in patients with peripheral IV devices the reported incidence of bacteraemia was between 0.2 and 0.5%, whereas in patients with CVC the number of bacteraemias increased to between 3.8 and 12%. Goldman and Maki (1973) reported that 7% of patients having total parenteral nutrition developed bacteraemias.

In a multi-centre study, Nystrom *et al.* (1983) investigated 10,616 surgical patients. Of these patients, 63% had an IV device *in situ* at some stage of their hospital stay. Overall 10.3% had a device-related thrombophlebitis and 0.37% of patients with peripheral cannulae and 4.48% with a CVC developed a hospital acquired bacteraemia. This was in comparison to only 0.05% of patients without an IV device who developed a hospital acquired bacteraemia. In comparison, Press *et al.* (1984) reported that in 922 patients with Hickman catheters, 14.4% had a catheter-related infection, and four patients died.

Within the United Kingdom, in 1991, almost 4,000 cases of catheter-related bacteraemia were reported to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (Elliott, 1993). This is probably a conservative estimate of the true infection rate due to under-reporting and difficulties in diagnosing catheter-related sepsis. From 1991 to 1994 there was a 32% increase in the number of reports of catheter-related sepsis. Indeed, in 1994 the incidence of catheter-related bacteraemias had risen to 5290 (unpublished data, PHLS). This change in incidence may be due to an increase in the number of IV catheters used as well as a greater awareness of the problem of catheter-related sepsis.

1.1   Types of intravascular catheters

The term IV catheter is very broad. There are many IV devices available each designed for a specific purpose. Figure 1-1 shows a typical triple lumen catheter and Figure 1-2 is an annotated diagram showing the various components of a triple lumen CVC. Table 1-2 highlights the types of devices available for central venous catheterisation and also states their uses.

Table 1-1   **Clinical problems associated with central venous catheters**

(Adapted from Elliott and Crocker, 1992).

Early Onset   Haemothorax

                                               Arterial/Venous damage

                                               Air embolism

                                               Pneumothorax

                                               Haematoma

                                               Subcutaneous emphysema

                                               Pleural effusion

                                               Cardiac perforation

Late Onset   Infection

                                               Thrombosis

                                               Endocardial damage

Figure 1-1   **A typical triple lumen central venous catheter**
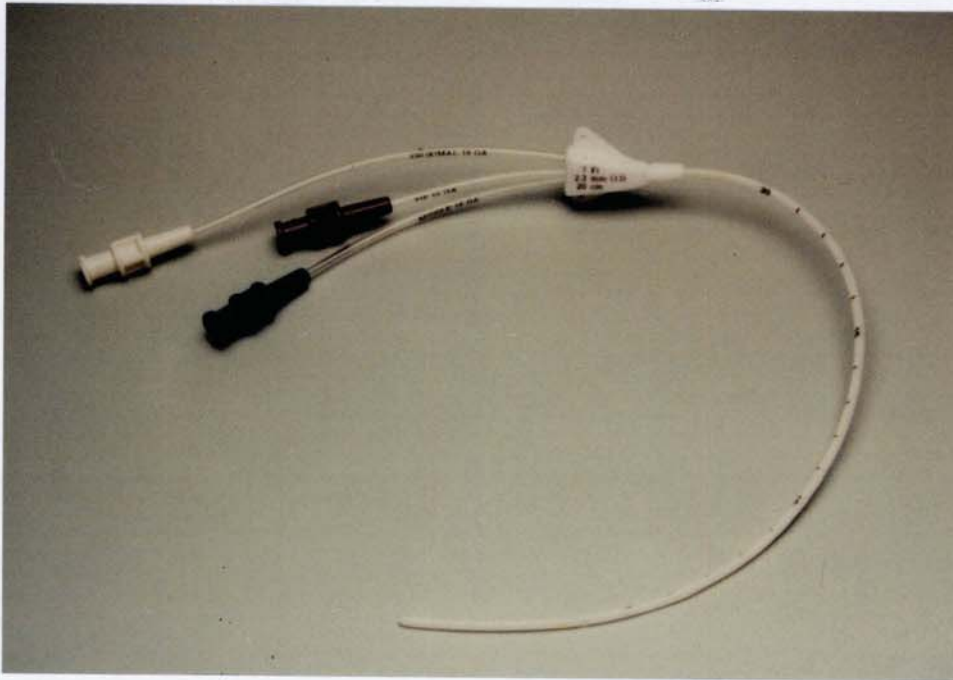
Figure 1-2   **An annotated diagram of a CVC**
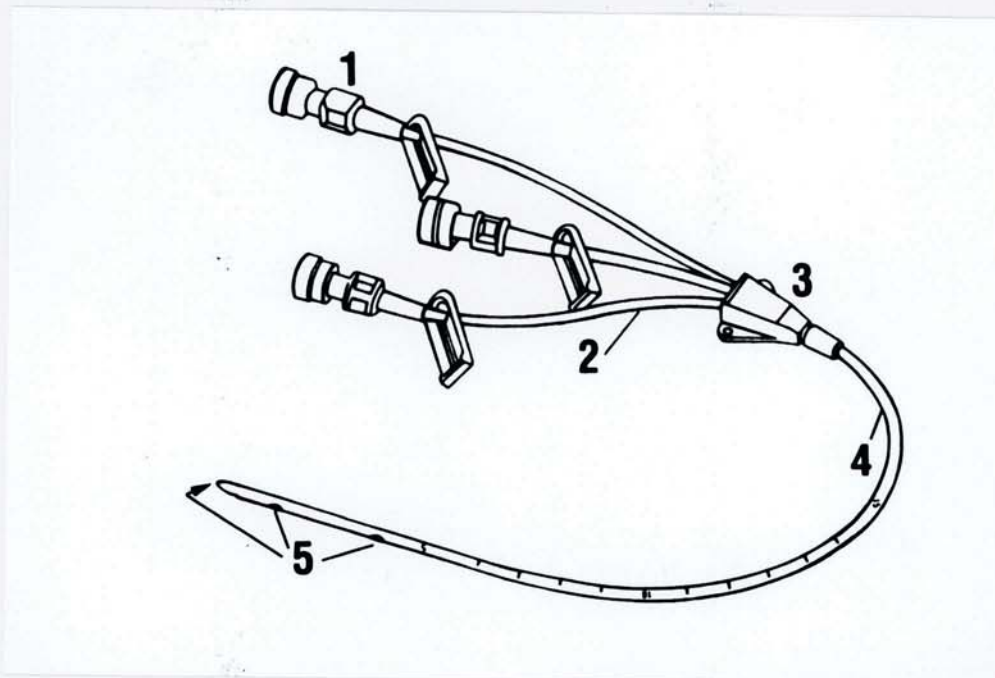
1. Catheter hub
2. Catheter side arm
3. Catheter junction boot
4. Catheter body
5. Lumen exit ports

Table 1-2   Types of intravascular catheters and their use

	DESCRIPTION OF CATHETER	CATHETER USE
SHORT TERM		
CENTRAL	Multi lumen	Drug/fluid administration Right heart monitoring
	Swan Sheath	Introducer sheath for a Swan Ganz catheter Rapid fluid infusion
	Swan Ganz	Cardiac output studies Left heart monitoring
	Haemodialysis	Haemodialysis Haemofiltration
PERIPHERAL	Arterial	Blood pressure monitoring Blood gas monitoring Blood sampling
	Venous	Drug/fluid administration
LONG TERM		
CENTRAL	Tunnelled (Hickman/Broviac) Non Tunnelled Implantable ports (Portacath)	All used for chemotherapy, drug/fluid administration venous blood sampling and total parenteral nutrition
	Peripherally Inserted Central Catheter (PICC)	Chemotherapy Drug/fluid administration Venous blood sampling Total parenteral nutrition

1.2 Infections associated with CVC

Infection is the most common recognised clinical complication associated with the use of CVC. Infection can either be localised around the CVC insertion site, or it may be systemic, affecting several body systems. The various clinical presentations and pathology of these infections are classified below:

1.2.1 Local infection

Localised infection can occur at the CVC skin insertion site. If the catheter is tunnelled the infection may track back along the subcutaneous channel. The presence of inflammation at the device insertion site may be an indicator that local infection has developed. However, the inflammation may be due to an adverse immunnological response to the CVC being recognised as a foreign body. Recent work (CVC audit study group, 1998 unpublished data) has suggested that the presence of two or more of the following is indicative of a localised CVC infection; erythema, oedema, cellulitis, phlebitis, clear exudate. The presence of purulent exudate or suppurative phlebitis is usually indicative of a local infection. Maki *et al.* (1977) when examining peripheral catheter local infection reported similar findings. Patients with localised CVC-associated infection may experience pain or discomfort arising from around the device insertion site. Figure 1-3 demonstrates local infection around a Hickman catheter skin insertion site.

1.2.1.1 *Types of phlebitis*

Phlebitis is inflammation of a vein and tends to lead to formation of a thrombus. Phlebitis may be caused by mechanical damage or biochemical irritation. Mechanical damage can occur if the device is not adequately secured by sutures and a dressing. Movement of the CVC can cause abrasion of the intima (Curelaru *et al*, 1983). Many drug infusions are also known to cause venous irritation, however this is uncommon in patients with CVC as these are placed in large vessels with high blood flow.

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1.2.1.2 *Suppurative phlebitis*

Suppurative phlebitis is a more serious form of CVC-related infection. This is usually found in catheters that have been inserted using a cut down technique and have been in place for greater than 48 h. Maki (1992) describes suppurative phlebitis as an intravenous abscess, discharging myriad's of microorganisms into the blood stream. Patients with suppurative phlebitis may subsequently develop an overwhelming septicaemia and the prognosis is usually poor.

1.2.1.3 *Thrombophlebitis*

Thrombophlebitis is inflammation of the vein with an accompanying blood clot. This can occur if the catheter bore size is similar to that of the catheterised vein therefore causing obstruction to blood flow. Blockage of the CVC may arise if a thrombus is formed. Thrombophlebitis may be accompanied by infection, a section of the thrombus may embolise resulting in haematogenous spread.

1.2.2 Systemic infection

Systemic infection associated with the use of CVC is present if any 2 of the following symptoms and signs are present:

Pyrexia following flushing of the CVC

Pyrexia unresponsive to broad spectrum antibiotics

No other obvious source of infection

Evidence of localised infection.

Microbiological evidence of CVC-associated infection

(Unpublished data - CVC audit study group)

Figure 1-3   Local infection around a Hickman catheter skin insertion site

1.3   Diagnosis of CVC-related infection

1.3.1   Clinical diagnosis of CVC-related infection

Any patient with a CVC *in situ* should be examined daily for clinical evidence of CVC-related infection. Signs of local or systemic infection should be investigated and treated where appropriate.

1.3.2   Laboratory investigations and diagnosis

There are 3 main microbiological approaches used to diagnose a CVC-related infection.

1) Blood cultures taken through the central venous device as well as from a separate peripheral venepuncture.

2) Microbiological culture of the CVC distal tip on removal of the device.

3) Skin swabs of the CVC insertion site on evidence of local infection.

1.3.2.1   *Blood Cultures*

It is generally accepted that if blood taken for culture from a CVC and from a separate peripheral venepuncture site contains identical microorganisms there is strong evidence that a CVC-related sepsis may be present (Elliott and Crocker, 1992). However other foci of infection can result in positive blood culture and care needs to be taken when interpreting these results. Wing *et al.* (1979) suggest that if blood taken through the CVC device contains more microorganisms than that obtained from a peripheral venepuncture then this is strongly indicative of a catheter-related infection. However other studies have demonstrated that there is no relationship between blood culture isolates obtained via a CVC and the subsequent microbiological results of the catheter segment (Graeve *et al.*, 1981., Maki *et al.*, 1973., Singh *et al.*, 1982).

1.3.2.2 *CVC distal tip analysis*

There are many laboratory based methods by which to determine CVC distal tip colonisation, these include broth cultures, vortex mixing, sonification, Gram staining and acridine orange staining. The most commonly used method to culture CVC distal tips was introduced by Maki *et al.* in 1977. A section of the CVC distal tip (2 to 3 cm) is rolled at least 4 times over the surface of a blood agar plate and the plate is then incubated for 24h at 37°C in air. Maki *et al.* (1977) proposed that a colony count of ≥15 colony forming units (cfu) is indicative of a catheter-related infection. It is, however, accepted that CVC may become contaminated with skin microorganisms when the device is removed prior to microbiological examination. To distinguish between infection and contamination Maki *et al.* (1977) suggest that a colony count of ≥15 cfu indicates a CVC-related infection, and a lower count represents contamination. The roll-plate method has met with much criticism (Collignon *et al.* 1986., Rello *et al.* 1991). It is argued that the original study (Maki *et al.* 1977) was based largely on the culture of short peripheral catheters and not CVC. The criterion is not universally accepted, many clinical microbiologists prefer to assess a culture result with direct reference to the patient's condition (Elliott. 1988). A further problem associated with the roll plate method is that only the external surface of the device is sampled. It has been demonstrated that microbial colonisation may occur on both the external and internal surface of the CVC (Cheesbrough *et al.* 1985).

To examine the internal surface of intravascular catheters Cleri *et al.* (1980) flushed the internal surface of intradermal and intravascular catheter segments with broth. It was reported that growth of > 1000 cfu from the internal surface of a segment was associated with bacteraemia. Kristinsson *et al.* (1989) when comparing the roll plate method for catheter culture with the internal flushing method reported a correlation between the two methods when the catheter was clinically considered to be infected. However cultures from the external catheter surface produced more false positive results.

The main problem associated with catheter culture is that the device has to be removed to allow a diagnosis of catheter-related sepsis to be made. Ryan *et al.* (1974) estimated that 75-85% of catheters are removed unnecessarily. A brush device that allows *in situ* sampling of the CVC may offer a solution to the problem of removal of non-infected

devices. A brush, which has a metal wire with a fixed plastic tip, has been developed to fit and slide within the catheter whilst it is *in situ*. The bristles of the brush are designed to pick up fibrin along the entire length of the catheter, from the hub to the distal tip. The brush tip can be cultured on removal thus making diagnosis without the CVC being removed (Tighe *et al.* 1996). However, there are some concerns regarding this method of catheter culturing. Firstly, there is a risk of inducing a post-brushing bacteraemia due to the release of microorganisms from the internal surface of the CVC into the blood stream. Secondly, there is potential for false positive results. The endoluminal brush, in order to pass down the CVC, has to pass through the catheter hub. It is well recognised that the catheter hub is one of the most common sites of origin for microorganisms leading to CRS (Linares *et al.* 1985., Sitges-Serra *et al.* 1985). Microorganisms may be picked up in the hub prior to the brush being passed through the catheter. There is at present, using this method, no mechanism by which to determine the point at which the brush becomes contaminated and therefore interpreting positive results may be difficult.

1.3.2.3 *Skin Swabs of the CVC insertion site*

Balakrishnan *et al.* (1991) noted a clear relationship between the microorganisms present at the insertion site and subsequent isolates obtained from the distal tips of catheters. Although skin swabs taken from the device insertion site may be helpful in predicting those at risk of infection (Syndman *et al.* 1982). Elliott (1993) reported that taking skin swabs from the device insertion site is probably only useful in patients where there is clear evidence of localised infection, as positive culture results may otherwise reflect the presence of skin commensals and could be misleading.

1.4   Source of microorganisms causing CVC-related infection

The main routes by which microorganisms gain access to catheters resulting in colonisation or CRS are shown in Figure 1-4. The various methods by which access is gained are discussed in detail below.

1.4.1   Extraluminal contamination

Wistbacka and Nuutinen (1985) reported that one of the main sources of contamination is the CVC skin puncture site. The microorganisms at this site can be either the patient's own endogenous flora or exogenous from the environment, including the medical practitioner. Bacteria on the patient's skin may migrate from the insertion site down the intra-cutaneous tract on the external surface of the CVC. This in turn can result in colonisation of the distal tip. It has also been suggested that microorganisms gain access to the CVC at the time of insertion (Elliott, 1988). Microorganisms may become impacted onto the distal tip of the device as it passes through the patient's skin. Adequate skin preparation is therefore essential to reduce the risk of CRS.

1.4.2   Intraluminal contamination

Catheter hub colonisation may represent the most important source of microorganisms (Elliott, 1988). Microorganisms colonise the internal surface of the catheter hub and subsequently migrate to the distal tip of the CVC via the internal lumen. Sitges-Serra *et al.* (1984) reported an outbreak of IV device-related infections by coagulase-negative staphylococci (CNS). This was attributed to hub colonisation following manipulation by medical staff.

1.4.3   Contaminated infusates

Catheter colonisation and subsequent infection can also result from contaminated infusions. There has been a number of reported outbreaks of hospital acquired CRS associated with contaminated fluid (Centres for Disease Control, 1971., Phillips *et al.*

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1972., Meers *et al.* 1973). Maki and co-workers (1976) reported approximately 400 cases of bacteraemia caused by *Enterobacter agglomerans* and *Enterobacter cloacae* which were associated with the use of 5% Dextrose in water. Investigation revealed that the outbreak coincided with the introduction of a new elastomer-lined, screw-cap closure system. Bacterial strains implicated in the epidemic were found throughout the manufacturing plant and gained access to the interior of the screw-cap via cooling condensate after autoclaving (Mackel *et al.* 1975). Hospital personnel inoculated the bacteria into intravenous fluid bottles when inserting administration sets. Due to more stringent manufacturing processes the incidence of contaminated infusates is now low. It should be considered, however, that patients may be at risk of CRS from infusions prepared within the hospital including the pharmacy and ward areas.

1.4.4 Haematogenous spread

Haematogenous seeding of microorganisms from a distant site onto a CVC is rare (Elliott, 1993). This is more likely to be related to Gram negative bacilli following a bacteraemia/septicaemia from another source.

1.4.5 Microbial contamination of the CVC during the insertion procedure

It was suggested that microorganisms may become impacted onto the distal tip of CVC as the catheter passes through the skin. (Elliott and Crocker, 1992). This hypothesis was investigated further as part of this thesis (Chapters 2 and 3).

Figure 1-4   The main routes by which microorganisms gain access to catheters resulting in colonisation or CRS

Aston University

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(Elliott. 1988: reproduced with permission © Lippincott Williams & Wilkins)

1.5 Factors influencing the development of CVC-related infection

The incidence of CVC-related sepsis is affected by many factors. Henderson (1988) separated the risk factors for CRS into two groups, patient-related and hospital-related. Patient-related factors include age, altered host defence mechanisms, underlying disease and remote infections. Hospital-related factors include catheter type, catheter material, insertion site, type of placement, duration of insertion at any one site and the skill of the individual placing the device. The main factors influencing microbial colonisation of intravascular devices are shown in Table 1-3.

Table 1-3   The main factors influencing microbial colonisation of intravascular devices

Adapted from Elliott and Crocker (1992)

1   Patient-related

Skin preparation

Site and position of insertion

Type of insertion (indwelling and direct access)

Patient's underlying condition

Diameter of vessel catheterised

Duration of catheterisation

2   Medical personnel-related

Handwashing before insertion

Care and technique of insertion

Subsequent care of insertion site

Types of fluid passed *via* the device

3   Intravascular device-related

Design

Catheter material

Surface topography of catheter

Leachable substances from the catheter

Catheter diameter versus blood vessel diameter

Flow rate of infusion

1.6   Prevention of CVC-related infection

1.6.1   Catheter insertion

1.6.1.1   *Aseptic technique*

Aseptic technique both at the time of CVC insertion, and for all subsequent management is probably the most important factor in combating CRS. As discussed earlier, the skin flora has been implicated as the major source of microorganisms in CRS. The medical practitioner inserting the CVC must have meticulous hand hygiene and follow a strict aseptic technique, since microorganisms can be transferred from the practioner's hands to the patient.

1.6.1.2   *Skin preparation*

The patient's skin at the CVC insertion site should be cleaned with an appropriate antimicrobial preparation.   There are many suitable products available such as 70% isopropanol, povidone-iodine and chlorhexidine. Maki *et al.* (1991) in a prospective randomised trial studied three antiseptics used for disinfection of patients' CVC and arterial catheter skin insertion sites, a total of 668 catheters were studied. The patients were randomised to 10 % povidone-iodine, 70% isopropanol or 2% aqueous chlorhexidine.   The disinfectant was used on the skin insertion site prior to catheter insertion and for all subsequent site care every 48h thereafter.   Chlorhexidine was associated with the lowest incidence of local catheter related sepsis, 2.3 per 100 patients, followed by 7.1 and 9.3 for alcohol and povidone-iodine respectively.   Catheter-related bacteraemias were also fewer in the chlorhexidine group (0.5 *vs* 2.3 and 2.6). Maki *et al.*(1991) concluded that the use 2% aqueous chlorhexidine for cutaneous disinfection before catheter insertion and at subsequent site care can substantially reduce the incidence of CRS. The skin preparation should remain on the patients' skin for up to 2 minutes to allow the microbial load to be adequately reduced thereby minimising the risk of microorganisms contaminating the catheter on insertion.

1.6.1.3 *Prophylactic antibiotics*

The administration of prophylactic antibiotics at the time of CVC insertion has been studied with varying results. Ranson *et al.* (1990) failed to demonstrate that vancomycin prophylaxis reduced CRS in patients undergoing chemotherapy for malignant disease. However, Bock *et al.* (1990) reported that the administration of oxacillin significantly reduced the incidence of CRS. Raad *et al.* (1997) in a prospective crossover randomised trial of novobiocin and rifampin prophylaxis for the prevention of CRS in cancer patients treated with interleukin-2, reported a significant reduction in the incidence of CRS in the treatment group. The investigators also reported a reduction in the number of local catheter related infections. A negative aspect to the study was that 35% of patients enrolled to the study failed to tolerate the oral antibiotics due to severe nausea. Despite studies supporting the use of the administration of prophylactic antibiotics at the time of CVC insertion, this practice has not gained widespread acceptance in clinical practice. Concern has been expressed that the use of prophylactic antibiotics given on CVC insertion may encourage the emergence of resistance (Elliott *et al.* 1994).

1.6.1.4 *Site of insertion*

It has been reported that venous access catheters placed in the lower extremities especially in the femoral vein have high complication rates. Infection is a particular problem due to increased colonisation rates, cleaning difficulties both pre and post insertion due to skin folds. Dressing and inspection of the CVC site in the femoral route is also difficult (Johnson and Oppenheim, 1992., Henderson, 1988). Goldman *et al.* (1973) recommend that venous lines are inserted in the upper extremities. Conversely, Norwood *et al.* (1991) reported that a properly placed femoral catheter in which the site is appropriately managed is at no higher risk from infection than one placed in the upper extremities.

1.6.1.5 *Method of insertion*

The Seldinger technique is the recognised method of CVC insertion. This method allows for minimal handling of the CVC insertion equipment. It should also result in minimal trauma to the tissues surrounding the CVC insertion site which may be a risk factor associated with the development of CRS (Elliott et al. 1994., Soni, 1996).

1.6.1.6 *Tunnelling of the catheter*

The Broviac catheter introduced in 1973 (Broviac et al. 1973) and the Hickman catheter introduced in 1979 (Hickman et al. 1979) were designed to impede migration of bacteria toward the intravascular catheter segment by a combination of subcutaneous tunnelling of the catheter and the use of a built-in catheter cuff. Flowers *et al.* (1989) compared cuffed catheters to conventional catheters and reported that there was a significant reduction in catheter colonisation. However, Keohane *et al.* (1983) randomised 83 TPN patients to either tunnelled or non-tunnelled catheter groups. It was reported that tunnelled catheters did reduce the incidence of CRS but only when the catheters were being cared for by untrained personnel. When a nurse specialist was employed to care for patients receiving TPN the incidence of CRS was reduced in both catheter groups and the process of tunnelling the catheter had no significant impact on the incidence of CRS.

1.6.2   Catheter care

1.6.2.1 *Topical antiseptics*

Care of the CVC exit site is of great importance since many CRS develop in this area. The application of antiseptics is central to the reduction in the likelihood of infection. Tincture of iodine, for example, was widely recommended as the antiseptic of choice for both skin preparation prior to device insertion, and at subsequent dressing changes (Goldman *et al.* 1973., Simmons, 1982., Goldman and Maki, 1973). However, Maki *et al.* (1991) have since reported that the use of chlorhexidine, when applied to the skin insertion site prior to device insertion and at all subsequent insertion site care, can substantially reduce the incidence of CRS as compared to the application of 10% povidone and iodine and 70% isopropanol.

1.6.2.2 *Topical antibiotic ointment*

The application of topical antibiotic ointment to the CVC exit site has been associated with reduced bacterial colonisation and subsequent catheter associated infection (Kaye & Smith, 1988). Conversely Norderm (1969), in a randomised double blind trial, compared the efficacy of the daily application of an ointment containing bacitracin, neomycin, and polymyxin with a placebo ointment around the catheter insertion site. The antibiotic

ointment increased the duration of catheter life and reduced the number of bacterial isolates from the catheter cultures. However, it did not reduce the incidence of CRS. It was suggested that the alteration of the resident skin flora around the CVC skin insertion site by the application of the antibiotic ointment may lead to catheter colonisation with resistant bacteria which in turn may result in CRS. Within the group studied there were two strains of *Candida albicans* isolates in the antibiotic group but none in the placebo group.

1.6.2.3 *Dressings*

There are two groups of dressings which can be used on CVC entry sites. Sterile gauze, and transparent dressings. Sterile gauze until the 1980s was the dressing of choice for CVC, however, to allow CVC skin insertion sites to be visually inspected without the removal of the dressing, transparent dressings were introduced. These transparent dressings are semi-permeable, allowing the evaporation of water vapour, but at the same time providing a protective barrier from the outside. There have been, however, reports that some transparent dressings are associated with increased rates of exit site colonisation, infection and subsequent CRS (Conley *et al.* 1989., Dickerson, 1989). Katich and Band (1985) observed a substantial increase in *Staphylococcus aureus* exit site infections following the introduction of transparent polyurethane dressings in their hospital. The increase disappeared when they reverted to dry gauze dressings. High colonisation counts around the exit site appear to be related to the accumulation of blood and moisture underneath transparent dressings encouraging microbial overgrowth (Elliott, 1993). A meta-analysis reported that transparent dressings led to a threefold increased risk of CRS compared with gauze dressings (Hoffman *et al.* 1992). More recently however, there has been the introduction of highly permeable transparent dressings with increased water vapour transmission rates and these are not associated with higher rates of CRS (Maki *et al.* 1994).

1.6.2.4 *Duration of catheterisation*

Duration of catheterisation is one of the most important hospital-related risk factors for CRS (Hampton and Sheretz, 1988., Henderson, 1988., Elliott, 1993). It is recommended that CVC should be removed as soon as possible, this then reduces the risk of CRS. (Hampton and Sheretz, 1988). With increased length of catheterisation the risk of CRS rises due to an increased risk of local infection. Microorganisms have time to travel via the internal and external lumen, they also have time to colonise and cause infection. There is an association between the number of breaks in the closed IV administration system, and microorganisms gaining access to entry ports (Lee *et al.* 1988., Gurevich, 1989). Breaks in the closed system are necessary in order to allow drug therapy and other essential patient management to be carried out.

1.6.3 Catheter design

1.6.3.1 *Triple versus single lumen*

Yeung *et al.* (1988), in a study conducted over a twelve month period, demonstrated that patients with triple lumen catheters were at greater risk of infection than those with a single lumen catheter. This study echoed the findings of other investigators (Pemberton *et al.* 1986., McCarthy *et al.* 1987). Triple lumen catheters have a higher infection rate due to increased manipulation breaking the closed system, and multiple infusions via separate ports again allowing the closed system to be interrupted. Yeung *et al.* (1988) suggest that a triple lumen catheter should not be used when a single lumen would suffice.

1.6.3.2 *Catheter polymers*

The chemical composition of the CVC can influence bacterial colonisation. Ludwicka *et al.* (1984) studied the attachment of *Staphylococcus epidermidis* onto a number of materials. They reported that bacterial adhesion was greatest with hydrophobic polymers such as silicone. Botta *et al.* (1984) demonstrated that polyethylene endoscope material was more attractive to bacteria than polytetrafluoro-ethylene. Similarly, Ashkenazai (1984) reported that the affinity of bacteria for polyethylene was greater than teflon. Central venous catheters are commonly manufactured with a hydrophilic surface. On contact with blood hydrophilic surfaces will absorb water and the resulting hydrated

surface has a low free energy (Jansen and Brim, 1987). This may be a key factor in improving blood compatibility and thereby reducing the risk of thrombus formation and subsequent infection (Jansen and Brim,1987).

The surface topography of the CVC can also influence bacterial colonisation. Cheesebrough *et al.* (1985) reported that the initial stage of bacterial attachment is associated with surface irregularities with microorganisms predominately attaching to roughened areas. Surface irregularity has also been associated with increased thrombogenicity (Hecker and Scandrett, 1985) which is in turn associated with bacterial colonisation and subsequently infection. A smooth catheter surface discourages thrombus deposition, microbial adherence and subsequent catheter colonisation (Hecker and Scandrett, 1985). Tebbs *et al.* (1994) compared the surface topography of 5 polyurethane CVC. The catheters were examined by both scanning electron microscopy and laser profilometry. Each CVC was challenged with the organism *S. epidermidis* and the ability of the microorganism to adhere to each CVC was assessed. The results of the study suggested that CVC with a smooth surface, absent of surface defects may reduce the risk of bacterial colonisation and therefore the risk of CRS.

1.6.3.3 *Electrical catheter*

A more recent approach to CRS has been the use of an electrical charge to repel microorganisms (Crocker *et al.* 1992). An *in vitro* study demonstrated that an electrical current (10 µA) can block several mechanisms by which microorganisms gain access to intravascular devices, including both extra-and intra-lumenal routes (Liu *et al.* 1997). The findings from this study suggest that an electrical device may offer *in vivo* protection from microbial attachment and colonisation and thereby reduce the risk of potential colonisation and subsequent CRS.

1.6.4 Bonding of antibiotics to catheter polymers

In order to decrease the risk of catheter colonisation and subsequent CRS antibiotics have been incorporated onto catheter surfaces. Sherertz *et al.* (1993) using an animal model, investigated the ability of anti-infective compounds to prevent *S. aureus* catheter related infection. This study demonstrated that dicloxacillin, clindamycin, fusidic acid and chlorhexidine decreased the risk of infection compared with the control (uncoated) catheters. Three of the coatings (dicloxacillin, clindamycin and chlorhexidine) decreased the risk of infection even if inoculation of the catheters was delayed 48 to 96 h post catheter implantation. Interestingly, the catheters coated with dicloxacillin or clindamycin, after 48 h, did not exhibit a zone of inhibition however they were still less likely to be infected than control catheters. Sherertz and co-workers (1993) attributed this to either antibiotic being present on the catheter but below the threshold for detection, or that the quaternary compound used to bond the antibiotic to the catheter had an antimicrobial effect independent of antibiotic activity. Jansen *et al.* (1992b) loaded 'Hydrocath®, CVC with the glycopeptide teicoplanin. Catheters were immersed in teicoplanin solution and, due to the hydrophilic surface coating, teicoplanin was absorbed by the surface layer. It was reported that teicoplanin loaded catheters, *in vitro*, did not initially eliminate bacterial adherence. After periods of up to 48 h however adherent viable bacteria were eliminated from the catheter surface by teicoplanin released from the catheter. It was noted that re-adhesion of bacteria occurred after 72 h. With re-adhesion of bacteria on the catheter surface occurring at 72 h this catheter may, in clinical practice, have the ability to reduce the risk of early onset CRS, however has little application in preventing colonisation and subsequent infection that can occur after this time period. Bach *et al.* (1996) who also assessed the retention of the antibiotic teicoplanin on hydromer coated CVC, reported that after 36 h of IV catheterisation no antibiotic was retained on the catheter when used *in vivo*. Although many researchers have investigated the role of antibiotic coated CVC (Table 1-4) with favourable results, their use clinically may be limited due to the possibility of encouraging the emergence of resistant microorganisms.

Table 1-4   Bonding of antibiotics to polymers for the prevention of catheter related sepsis
Adapted from Jansen (1997)

Polymer	Antibiotic	Determination of antimicrobial activity	Reference
Polyurethane	Dicloxacillin	Mouse model	Sherertz *et al.* 1989
	Clindamycin Fusidic acid Ciprofloxacin Cefuroxime Cefotaxime	Rabbit model	Sherertz *et al.* 1993
	Clindamycin Flucloxcacillin Vancomycin Ciprofloxacin	*In vitro* colonisation	Jansen *et al.* 1987
	Teicoplanin	*In vitro* colonisation *In vivo* CRS and colonisation	Jansen *et al.* 1992b Bach *et al.* 1996
	Minocycline & Rifampin	*In vivo* CRS and colonisation	Raad *et al.* 1997
Silicone	^{14}C-Benzylpenicillin Teicoplanin & Vancomycin	Rat model *In vitro* colonisation	Trooskin *et al.* 1985 Wilcox *et al.* 1994
Polyethylene	Cefazolin	*In vivo* CRS and colonisation	Kamal *et al.* 1998

1.6.5 Bonding of antiseptics to catheter polymers

To reduce the risk of the emergence of antibiotic resistant bacteria which may occur with antibiotic coated CVC, antiseptics have been incorporated into catheter polymers.

It is believed that the widespread emergence of antiseptic resistant microorganisms is unlikely due to the antiseptic action mechanism occurring through basic chemical reactions, unlike antibiotic action mechanisms which are generally under genetic, and hence, mutatable and plasmid-transmissable control (Russell *et al.* 1986., Civetta, 1996).

1.6.5.1 *Irgasan*

Antiseptic bonding to catheter polymers has been documented from as early as 1986. Kingston *et al.* (1986) incorporated the antiseptic irgasan into plastics discs and demonstrated a reduction in associated infection in rabbits. Further studies by Kingston and colleagues (1992) conducted on baboons reported that although irgasan could be incorporated into plastics, and it was effective against *S. aureus* and *S. epidermidis*, it was released too rapidly from polyurethane cannulae to be of value in clinical practice.

1.6.5.2 *Iodine*

Jansen *et al.* (1992a) incorporated iodine into the hydrophilic Hydromer® catheter, however, they reported similar findings to Kingston and colleagues (1992). Although the catheter was effective at the time of antiseptic release, microbial colonisation occurred when the release of iodine was exhausted. This product was used for in vitro studies only.

1.6.5.3 *Chlorhexidine gluconate and silver sulfadiazine*

To date only one antiseptic bonded catheter has been fully evaluated in clinical practice. This polyurethane catheter has been impregnated with chlorhexidine gluconate (0.75 mg) and silver sulfadiazine (0.70mg) on the external surface (ARROWgard™). The clinical trials conducted using this CVC have produced varying results. Maki *et al.* (1997) who studied 158 intensive care patients with a total of 442 catheters reported that antiseptic catheters were less likely to be colonised at the time of removal in comparison to control

non-antimicrobial catheters (13.5 compared to 24.1 per 100 catheter days), and were nearly fivefold less likely to produce bloodstream infection. These results have been echoed by other workers when similar studies have been conducted within the intensive care environment (Ramsey *et al.* 1994., Raymond and Steinberg, 1994., Trazzera *et al.* 1995., Lovell *et al.* 1995). Maki and co-workers (1997) in their study concluded that: the chlorhexidine-silver sulfadiazine catheter was tolerated by patients, the incidence of catheter related infection was reduced, the time noncuffed impregnated CVC could remain in place was extended and that cost savings could be made if the device were used. Although Maki and colleagues provided encouraging data some interesting questions can be raised regarding the study methodology. The skin disinfectant used prior to the insertion of the study CVC and at all subsequent site care was 10% povidone-iodine. The use of povidone-iodine had previously been reported by the same author as not being as effective as 2% aqueous chlorhexidine when used for skin disinfection prior to CVC insertion and at post insertion site care (Maki *et al.* 1991). Although both study groups received the same skin preparation it could be argued that the catheters may have been challenged by an unnecessarily high microbial load. This high microbial load however may be one which the test catheter may have been expected to overcome in the early stages of catheterisation. It was not stated within the study whether prior to the removal of the study CVC the catheter skin insertion sites were cleaned with an antiseptic. If the skin insertion sites were not cleaned this may have some bearing on the external surface colonisation rates as the devices may have become contaminated with skin pathogens during the removal process. Details of the time taken between CVC removal and microbiological processing and/or storage conditions of the specimens were not stated. If the catheters were not processed immediately the action of the antiseptic catheter may have continued despite having being explanted. If the catheters were not stored at 4°C prior to processing microorganisms present on the control CVC may have continued to multiply whilst microorganisms on the test catheter may have been inhibited by the antiseptic present on the CVC surface. Intraluminal contamination has been clearly demonstrated to be a major source of microorganisms causing CRS (Sitges-Serra *et al.* 1984). It has been suggested that the catheter hub may represent the most important source of these microorganisms (Elliott, 1988). The study conducted by Maki and colleagues (1997), with the chlorhexidine and silver sulfadiazine impregnated CVC

reported hub colonisation rates of more than 10 cfu/ml in 23.1% of its control catheters and 26.4% of the test CVC, however, the internal lumen of the CVC were not analysed for microbial colonisation. The test CVC had antiseptic coating on the external surface only.

The chlorhexidine and silver sulfadiazine impregnated CVC has been reported to significantly reduce the incidence of CRS in patients within an intensive care environment (Maki et al. 1997). Conversely, when the antiseptic impregnated catheter was used in highly immunocompromised patients, for example those with haematological malignancy, the results were not as favourable. Ellis et al. (1996) reported that of 11 assessable catheters studied 8 developed mechanical dysfunction which lead to the removal of 2 devices. Two patients developed exit site infections, and 3 further patients developed probable bacteraemia. These infection rates, when combined, gave an overall incidence of catheter related infection of 45%. This study was terminated due to what was viewed as an unacceptably high rate of mechanical dysfunction and infection. Logghe et al. (1997) in a double blind randomised trial studied a total of 680 CVC in patients with haematological malignancy. Logghe and colleagues (1997) reported that there was no statistically significant difference between the overall rates of bloodstream infection for antiseptic impregnated and non-impregnated catheters. The incidence of CRS was very similar in both groups (5.0% compared to 4.4%) as was the time to onset of bacteraemia. Logghe and co-workers, from their study, concluded that the chlorhexidine and silver sulfadiazine impregnated CVC neither reduced the risk of bloodstream infections nor delayed their occurrence in patients with haematological malignancy. It can be seen from the clinical studies carried out to date that the chlorhexidine and silver sulfadiazine impregnated CVC reduces the incidence of CRS and bacteraemia in those patients who require short term central venous catheterisation, however the use of such CVC in those patients who require catheterisation for longer periods appears, to date, unwarranted. The difference in the documented incidence of CRS in haematological patients and intensive care patients may be due to the mean length of time the CVC remained in situ. Logghe et al. (1997), in the haematology patients they studied, reported the mean length of time CVC remained in situ was 20 days, and that CRS did not occur until the CVC had been in place for upto 5 days. Logghe and colleagues argue that the lack of antiseptic on the internal surface of the chlorhexidine and silver sulphadiazine CVC is the reason why,

in their study, CRS was not prevented. Hub colonisation represents an important source of microorganisms in the development of CRS, however, microorganisms transferred *via* the internal route may require up to 5 days to become clinically significant. Maki and colleagues (1997) in their study reported the mean duration of catheterisation as 6 days. This considerable shorter catheterisation period in Maki's study, coupled with the internal surface of the study CVC not being assessed, may account for the more favourable results when chlorhexidine and silver sulphadiazine catheters are used in intensive care patients.

Darouiche *et al.* (1997) in a multicentre randomised trial compared the chlorhexidine and silver sulfadiazine catheter to a CVC bonded with the antibiotics minocycline and rifampin. In this study the catheters bonded with antibiotics were demonstrated to be three-fold less likely to be colonised by microorganisms than those in the antiseptic CVC group and were 12 fold less likely to produce catheter related bloodstream infection. The authors reported that CVC impregnated with minocycline and rifampin were significantly more effective at preventing CRS when compared to CVC impregnated with chlorhexidine and silver sulfadiazine, the authors however did not address the issue of antibiotic resistance.

From the clinical studies conducted to date there have not been any catheter related adverse effects reported when the chlorhexidine and silver sulfadiazine impregnated CVC has been used. Maki *et al.* (1997) reported that erythema at the CVC skin insertion site occurred more frequently in the test group however in the majority of cases the erythema was mild. There were no reported cases of hypersensitivity or toxicity during the course of the study. More recently however there have been reported cases of immediate systemic hypersensitivity to chlorhexidine and silver sulfadiazine impregnated CVC (FDA, 1998). The Food and Drink Administration, USA (FDA) issued a public health notice advising that anaphylactic type adverse events had been noticed while using the impregnated CVC. The adverse events were only recorded in Japanese patients and it was suggested that this population may have a genetic predisposition to react to these chemicals, or may have a heightened sensitivity to chlorhexidine due to an over exposure to this antiseptic which is present in many medical products. Complications associated with the chlorhexidine and silver sulfadiazine impregnated CVC has led to the manufacturers of the product withdrawing it from the Japanese healthcare market.

1.6.5.4 *Benzalkonium chloride*

The quaternary ammonium compound, benzalkonium chloride (BZC), is widely used within healthcare both as an antiseptic and a preservative. Benzalkonium chloride is used for pre-operative skin disinfection of unbroken skin, application to mucous membranes and for bladder and urethra irrigation. Benzalkonium chloride is used in nappy rash creams and included in lozenges for the treatment of superficial mouth and throat infections (Hugo and Russell, 1992). As a preservative, in the United Kingdom, BZC is one of the recognised antimicrobial agents suitable for use as an eye drop preservative and is also included in hard contact-lens cleaning solutions (Hugo and Russell, 1992).

Webb et al. (1986) incorporated BZC into polytetrafluoroethylene vascular grafts and demonstrated that it inhibited bacterial adhesion. More recently Tebbs and Elliott (1993) investigated the efficacy of BZC when it was incorporated into CVC. Benzalkonium chloride was incorporated into both the internal and external surface of Hydrocath® triple lumen catheters and the antimicrobial activity assessed *in vitro*. Tebbs and Elliott (1993) determined bacterial adherence to these catheters in both a static broth and a dynamic model. The dynamic model represented a catheter with a continuous flow of fluid around it. The isolates used in the assessments included both Gram-positive and Gram-negative microorganisms and the yeast *Candida albicans*. It was reported that bacterial adherence to the BZC impregnated catheters was significantly reduced as compared to control catheters. Gram-positive bacteria were less able to adhere to the CVC as compared to yeasts and Gram-negative microorganisms. Despite some yeasts and Gram-negative microorganisms adhering to the test catheter surface, the numbers were significantly fewer as compared to the uncoated control CVC. The catheters impregnated with BZC were shown to have antimicrobial activity for up to 14 days when they were immersed in phosphate buffered saline and for 7 days when immersed in 25% human blood. It was suggested that the decreased antimicrobial activity over time from the catheters when they were immersed in blood may have been due to the presence of protein as, the activity of many quaternary compounds is reduced in the presence of protein (Hugo and Russell, 1992). Despite a reduction in the number of days the BZC remained antimicrobially active in the presence of blood, Tebbs and Elliott (1993) conclude that the BZC impregnated Hydrocath® catheter may have a potential role for use in clinical practice.

Further work by Tebbs and Elliott (1994) comparing bacterial adherence to CVC with and without hydrophilic coatings to that of a hydrophilic CVC impregnated with BZC demonstrated that hydrophilic coated CVC did significantly reduce the adherence of bacteria to the external catheter surface in 3 out of 5 *S. epidermidis* strains studied. Indeed, if the catheter had both a hydrophilic external surface and was impregnated with BZC bacterial colonisation was further restricted. The number of *S. epidermidis* which adhered to the internal surface of the BZC impregnated hydrophilic catheters was also significantly reduced compared to the number which adhered to the polyurethane catheters.

The results from these *in vitro* studies (Tebbs and Elliott, 1993., 1994) clearly demonstrated that BZC impregnated into hydrophilic CVC was effective in reducing both Gram-positive and Gram-negative bacterial colonisation. The CVC impregnated with BZC has subsequently been developed for clinical use, and results from the *in vivo* study are presented as part of this thesis.

1.6.6   Bonding of heparin to catheter polymers

Heparin is bonded to the surface of most pulmonary artery flotation catheters during the manufacturing process, this is to reduce thrombosis after the catheter has been inserted (Hoar et al, 1981). It has been suggested that pulmonary artery catheters once bonded with heparin do reduce the risk of CRS (Mermel *et al.* 1993). Heparin is bonded to the pulmonary artery catheter surfaces using BZC. Benzalkonium chloride has antimicrobial properties and therefore it is likely that the anti-infective mechanism of pulmonary artery catheters is a result of the BZC rather than heparin. Elevated serum sodium and potassium levels have been reported when blood samples were taken through heparin-bonded umbilical catheters. The umbilical catheter studied had heparin bonded to the device through a process using BZC (Gaylord *et al.* 1991). The authors reported that although the measured BZC released from the umbilical catheter was of low concentration, clinical errors may occur due to fictitious sodium and potassium levels. It was considered that the erroneous readings were due to misreadings by some ion selective electrodes. There have not been any reports, to date, of raised serum sodium and

potassium levels when serum samples have been taken through heparin-bonded catheters used in adults.

1.6.7 The incorporation of silver into catheter polymers

Silver has a broad spectrum of antimicrobial activity and is of minor toxicity (Jansen, 1997), for these reasons silver has been impregnated into medical devices including urinary catheters (Johnson *et al.* 1990). The use of silver for the prevention of intravascular CRS was first introduced by Maki *et al.* (1988). Maki and colleagues developed a subcutaneous cuff constructed of a biodegradable collagen matrix impregnated with bactericidal silver. The cuff was designed to be positioned 0.25 - 0.75 cm below the CVC skin insertion site and was positioned over the catheter guidewire during the CVC inplantation process. The purpose of the cuff was to prevent microorganisms migrating from the CVC skin insertion site to the catheter distal tip *via* the external surface of the device. Despite the silver impregnated CVC cuff reducing catheter colonisation by a third, this technology is not being widely used.

More recently silver has been incorporated into CVC polymers. Goldschmidt *et al.* (1995) investigated the efficacy of a silver-coated polyurethane CVC when used in oncology patients. The authors reported a 50% reduction in the number of CRS observed in the study group as compared to the control and there were no reports of adverse reactions to the silver coated catheter. The use of silver as a means of reducing catheter colonisation is being employed by many catheter manufacturers in order to reduce the incidence of CRS. Some manufacturers have combined silver with other antiseptics, for example chlorhexidine (Maki et al. 1997). More recently, catheter polymers have been developed which, by iontophoresis, release silver ions from the device surfaces (Vygon, 1998). At present there are no data available regarding the efficacy of this newly developed catheter when it is used in clinical practice.

1.7   Cost analysis

The concept of value for money in health care has recently become very important within the National Health Service (NHS). Different methods of economic evaluation have been employed to ensure value for money is achieved. Economic evaluation is a technique developed by economists to assist in decision making when several courses of action could be taken. The main methods of economic evaluation are: cost-minimisation analysis, used when the outcomes of the procedures being compared are the same; cost-effectiveness analysis, used when the outcomes may vary but can be expressed in common natural units such as mmHg for treatments of hypertension; cost-utility analysis, used when outcomes vary, for example quality of life scales; cost-benefit analysis, when a monetary value is being placed on services received (Robinson, 1993a).

The concept of cost-benefit analysis was introduced over 50 years ago and is the most widely recognised form of economic evaluation. In Britain it was applied widely in the 1960's, primarily to transport investment projects. Cost-benefit analysis has subsequently been used in a variety of areas including healthcare. Within the healthcare sector, attaching a monetary value to outcomes is a useful indicator of cost-benefit for a particular procedure or programme (Robinson, 1993b). Benefits may be direct or indirect. For example, the cost of surgery, the savings achieved by the avoidance of hospitalisation or the productivity gains through return to work can all be evaluated. For this type of analysis monetary value has to be placed on both sides of the cost-benefit equation. Benefits are often expressed in terms of rates of pay. However, in this method patients who are unemployed are not fully assessed. Placing a monetary value on peoples' lives has raised strong ethical objections. However, economists argue that valuations of human lives are used in a wide range of decisions about allocation of resources in the public sector (Jones-Lee, 1976., Mooney, 1977). Within healthcare it is not always possible to express benefits in terms of monetary value. Benefits within healthcare can also be expressed in terms of quality of life for example being pain free, achieving mobility and retaining the ability to fulfil the activities of daily living.

1.7.1 Cost of antimicrobial therapy

Intravenous antimicrobial agents are reported to account for 30 to 40% of the total pharmacy drug acquisition budget (Guglielmo and Brooks, 1989). The overall cost of antimicrobial therapy is difficult to quantify. The acquisition cost is often the factor used in determining the financial impact of any given course of treatment, however many other factors need to be considered (Table 1-5). The preparation and administration of many antimicrobials can occupy a large proportion of healthcarers' time. Furthermore, certain antimicrobials that are relatively inexpensive to purchase, for example gentamicin, may be costly in terms of serum level monitoring. Plasma aminoglycoside concentrations and serum creatinine levels are commonly used in monitoring gentamicin therapy.

Any consideration of the cost of antimicrobial therapy, must also account for complications that may be associated with the therapy. Eisenberg *et al.* (1987) studied the cost of nephrotoxicity associated with aminoglycosides. The study reviewed 1756 patients who received aminoglycosides, and of these patients 129 (7.3%) developed aminoglycoside-associated nephrotoxicity. The mean total additional cost of aminoglycoside-associated nephrotoxicity was calculated using hospital accounting methods and was reported to be $US 2501 ($183 per patient receiving aminoglycosides).

Table 1-5   Cost factors associated with the use of antimicrobial therapy in the hospital setting

1.   Acquisition costs

      Purchase price - can be discounted by bulk buying and careful negotiations

2.   Preparation costs

      Personnel labour; pharmacist, nurse, MLSO

      Materials; 70% isopropanol, swabs, needles, syringes

3.   Drug administration costs

      Labour

      Intravenous sets, infusion pumps

4.   Storage of drugs and equipment

5.   Antimicrobial monitoring costs

      Labour (taking of serum, transportation of specimens, laboratory staff)

      Laboratory tests

6.   Cost of toxicity

      Allergic reaction

      Bone marrow suppression

      Nephrotoxicity

7.   Failure of therapy

Adapted from Guglielmo and Brooks, 1989

1.7.2 Methods of reducing the costs associated with infection and antimicrobial therapy

Several approaches have been employed to reduce the cost associated with antimicrobial therapy in the treatment of various infections, these include:

1.7.2.1 *Therapeutic equivalence*

Two agents are considered therapeutically equivalent if they have a similar spectrum of activity, efficacy and adverse effect profile (Guglielmo and Brooks, 1989). The relatively less expensive drug can be selected. Schwinghammer *et al.* (1985) for example reported substantial savings when the use of tobramycin was substituted for gentamicin.

1.7.2.2 *Monotherapy versus combination therapy*

Malek *et al.* (1992) compared the cost of ceftazidime monotherapy to gentamicin and β-lactam combinations. The study was carried out in three UK hospitals. The results demonstrated that ceftazidime had a relatively high acquisition cost as compared to the combination therapy. However the combination therapy group incurred greater overall costs due to the need for additional materials used in drug administration and serum antibiotic assays. The average drug and equipment costs for ceftazidime administration was reported to be £230.13 compared to £253.94 for gentamicin with a β-lactam. Malek *et al.* (1992) also reported that personnel time spent on drug administration and assays was less in the ceftazidime group at 1 h 43 min. compared to 4 h 57 min in the gentamicin group. Other studies also concluded that monotherapy is efficacious and results in considerable cost savings (Briceland *et al.* 1988., Pizzo *et al.* 1986).

1.7.2.3 *Long-acting agents*

Cost savings can be made by reducing the number of drug administrations in a 24h period. Tanner and Nazarian (1984) projected cost savings of between $US28 to $145 when a 10 day course of parenteral antimicrobial therapy was changed from a 6 or 8 hours dosing schedule to a single daily dose. This study also highlighted the cost of antimicrobial preparation and administration.

1.7.2.4 *Route of administration*

Changing the route of drug administration can reduce costs. Quintiliani *et al.* (1986) reported that when patients with infections have responded clinically to initial intravenous antimicrobial therapy, a subsequent change from parenteral to oral therapy can reduce costs significantly. Patients receiving oral therapy may also be discharged from hospital earlier, thereby reducing the overall cost of the hospital admission.

1.7.2.5 *Restricted formularies*

A restricted formulary, which limits antibiotic use to be selected on criteria such as therapeutic equivalence, monotherapy, route of administration, can encourage not only good clinical practice but also ensure cost efficiency. There is a need for regular education to ensure restricted antimicrobial systems are applied in the hospital environment.

1.7.3 Costs of infection

The prevalence of infection acquired by patients after admission to hospital is approximately 10% and result in both increased mortality and morbidity, and a prolonged hospital stay. This represents a relatively large financial burden for The National Health Service (DOH and PHLS. 1995). Ayliffe and Collins (1982) estimated that if 5% of patients were to acquire a nosocomial infection which resulted in their spending three extra days in hospital, then the cost to the NHS would be £30 million. This figure excluded the cost of antibiotics, dressings, increased microbiology tests and the need for additional primary care facilities on patient discharge from hospital.

The management of post-operative wound infections consume a high proportion of the hospital budget. O'Donoghue and Allen, (1992) reported an outbreak of wound infections in an orthopaedic ward involving 10 patients. The infected patients had on average an increased hospital stay of 17 days which overall incurred costs of £2220 per patient. This figure did not include the costs associated with the outbreak investigation. The increase in hospital stay associated with nosocomial infection varies according to the speciality studied. Coello *et al.* (1993) reported an overall increase in hospital stay of 8.2

days due to hospital acquired infection in surgical patients. This increase in hospitalisation varied from 3.0 days for gynaecology, 9.9 days for general surgery and 19.8 days for orthopaedic patients. Similar periods of prolonged hospital stay have been reported in other studies (Davies and Cottingham, 1979., Green *et al.* 1982).

Liu-yi and Shu-qun (1990) studied the economic effects of nosocomial infections in cardiac surgery. Patients who underwent cardiac surgery over a 1 year period were admitted into the study. Infected cases were matched with uninfected patients treated during the same time period using the following data: sex, age, underlying disease, surgical procedure, and length or pre-operative stay. Of 1207 patients studied 7.4% acquired a nosocomial infection. The overall additional cost per patient was £290. The mean additional costs of £782 were particularly high in patients who developed multi-site infections. Lower respiratory tract infections also proved to be more costly than post-operative wound infections. Infected patients in this study were in hospital for a mean of 14 extra days and on this basis, the additional costs reported in this study appear to be relatively low compared to those discussed earlier (O'Donoghue and Allen, 1992). This demonstrates the difficulty in interpreting cost analysis studies when health care systems differ.

The cost of infection should not only be considered in monetary terms. There are also human and other non-financial costs associated with hospital acquired infection. The patient may suffer increased morbidity with pain due to the infection and be separated from their family and the community for an increased period of time. Increased family support may also be necessary on the patients discharge from hospital.

Increased length of hospital stay is one of the most important costs of hospital acquired infection. The prolonged length of stay for one patient may delay a further patient from receiving treatment. Davey *et al.* (1991) suggest a complete analysis of human and non-financial cost of hospital acquired infection should take into account the suffering of patients whose treatment is delayed as well as that of the patients with infection.

A reduction in the number of hospital acquired infections may, depending on the health care setting, not have any real impact on hospital finances. Daschner (1989) reported that

hospital administrations in Germany have no interest in reducing nosocomial infection rates and thus the length of hospitalisation because insurance companies pay the same amount of money for each day of hospitalisation. Following the introduction of the NHS reforms in the UK (DOH, 1989) contracts for hospital services were introduced and this may have had some impact on the attitude towards the need to reduce hospital acquired infections. Hospital trusts have contractual obligations to fulfil and these include the number of patients to be treated. Consequently, an increased length of hospital stay due to hospital acquired infection may reduce the throughput of patients within hospital and hence the ability of the hospital to meet its contract requirements.

1.7.3.1 *Costs of CVC-associated infection*

The cost of CVC-associated infections has not previously been accurately determined. The Kings Fund Centre (1992) reported an estimated cost of a CVC-related infection between £1650 and £5000. These figures were estimated using 2 case scenarios. The first, a patient with a 7 day increased hospital stay due to CVC-associated infection who was nursed on a general ward. The patient had their CVC removed due to an associated infection, antimicrobial treatment was also given. The second patient had a increased hospital stay of 10 days and needed high dependency care due to CVC associated sepsis, thereby increasing costs. The patient had their infected CVC removed and replaced. Antimicrobial therapy was more complex in the second scenario due to a resistant microorganism. The cost estimated included: the crude price of hospital bed per day; bacteriology tests; antimicrobial therapy and intravenous fluid disposables. The estimations made were very broad and a large number of presumptions were made. To determine the absolute cost of a CVC-related infection a more accurate method would have to be employed encompassing all hospital costs.

1.8 Aims of the study

Central venous catheters have become an integral part of patient management, however, they are associated with many complications of which infection is the most common. Infections associated with CVC can be either local at the skin insertion site or systemic. Despite efforts being made to reduce the incidence of CRS the problem continues to rise (PHLS, Unpublished data). The major source of microorganisms causing CRS have been documented to be either from the patient's own skin flora or from the operator inserting and caring for the device (Elliott, 1988). The routes of microbial spread are both extraluminal along the external surface of the catheter or intraluminal from the catheter hub. Preventative measures have been employed in order to reduce the incidence CRS as not only do these infections have an associated morbidity and mortality they also have resource implications for the healthcare system.

The aims of this study are:

1/ To investigate the skin as a source of microbial contamination at the time of CVC insertion.

2/ To examine the role of needleless connectors in the development of CRS.

3/ To determine the cost incurred by patients whilst hospitalised due solely to an infection associated with a CVC.

4/ To study the efficacy of an antimicrobial impregnated CVC in the prevention of catheter colonisation.

2. Determination of whether CVC become contaminated with microorganisms on insertion.

2.1 Introduction

There are 5 main sources of microorganisms which cause catheter related sepsis (CRS):

a) Extraluminal spread (Elliott, 1988), in which microorganisms present on the skin surface migrate extraluminally, down the percutaneous tract, to the distal tip of the catheter.

b) Intraluminal contamination (Sitges-Serra *et al.* 1984) may occur in which microorganisms present in the catheter hub migrate down the internal surface of the catheter to the distal tip.

c) Contaminated infusates may also be a source of microorganisms which cause CRS (Phillips *et al.* 1972., Meers *et al.* 1973). Contaminated intravenous infusions are administrated *via* the catheter which may lead to septicaemia.

d) Haematogenous seeding of organisms from a distant site can also occur (Elliott, 1993). These two latter sources could be considered to be of minor importance as compared to the external and internal routes.

e) Microorganisms may become impacted onto the distal tip of the CVC as the catheter passes through the skin at insertion. This possible source of CVC-associated sepsis investigated further in this thesis.

There were three objectives in this part of the study. Firstly to investigate the efficacy of skin disinfection prior to CVC insertion. The second objective was to determine whether the components of CVC insertion sets become contaminated with microorganisms during the cannulation procedure. Thirdly the study was designed to determine whether

microorganisms are impacted onto the CVC distal tip when the catheter penetrates the skin during insertion.

2.2   Materials and Methods

Thirty patients undergoing coronary artery bypass grafting or cardiac valve replacement procedures at the Queen Elizabeth Hospital, Birmingham were recruited into the study following informed consent. These patients were due to receive a CVC as part of their medical treatment. The patients recruited had the distal tip of their CVC sampled for microbial contamination whilst *in situ*. The associated insertion equipment was also examined for the presence of microorganisms.

2.2.1   CVC insertion

A full aseptic technique was employed by the medical staff during the CVC-insertion procedure.   The catheter skin insertion site and surrounding area was sprayed with chlorhexidine gluconate 2.5% in industrial methylated spirit (IMS) (DuPuy Healthcare, Leeds, UK), and allowed to dry for 2 minutes. Sterile drapes were then placed around the CVC-insertion site and associated non-clean areas. The triple lumen polyurethane, 30cm, 7 Fr catheters (Deltacath[*] Becton Dickinson, Meylan, France) were inserted by a Seldinger technique (Soni, 1996) to a distance of 25-30 cm, into the right atrium. This depth was selected to allow the distal portion of the CVC to be sampled during surgery.

2.2.2   Determination of microbial contamination of the CVC insertion equipment.

All the components of the CVC-insertion set including the introducer needle and cannula, guidewire, dilator and scalpel, were collected after use in a sterile container and assessed for microbial contamination. All the components, except the scalpel blade, were cut into 1 cm lengths . The segments of the introducer needle were added to 2 ml of Triton X-100 (0.05% in phosphate buffered saline) and vortex mixed for 60 s. Similarly, the segments of the cannulae, guidewires, and dilators were each added to 2 ml of Triton X-100 (0.05%

in phosphate buffered saline) and vortex mixed for 60 s. The scalpel blade was sampled by flushing 2 ml of Triton X-100 over the surface for up to 5 seconds, 10 times. Aliquots of 100 µl of the solutions were then plated onto 7% blood agar plates which were incubated for a 24h period at 37°C in 5 % CO_2. The plates were then assessed for microbial growth and microorganisms were identified by standard microbiological techniques including the API Staph System (API, Biomerieux SA Marcy-L'Etoile, France). Any plates without microbial growth were re-incubated for up to 96 h as above.

2.2.3 Evaluation of the number of microorganisms on the skin at the CVC insertion site

Immediately following placement of the CVC the $2cm^2$ area of the skin surrounding the catheter insertion site was swabbed to determine the number of microorganisms remaining on the surface of the skin. Applying a standard swabbing technique (Williamson and Kligman, 1969), a sterile cotton swab, moistened with Triton X-100 (0.1%) in phosphate buffered saline was used to sample the area. The swab was then placed in 2ml of Stuart's Transport Medium (STM) containing lecithin (2%) and Tween-80 (3%). The lecithin and Tween-80 neutralised any chlorhexidine present (Chawner and Gilbert, 1989). Triton X-100 (0.05%) was added to the STM prior to vortex mixing for 60s. Aliquots of 100 µl were made and analysed for the presence of any microorganisms as described above.

2.2.4 Sampling of the CVC distal tip whilst *in situ*

To facilitate coronary artery bypass grafting or valve replacement a patient has to be placed on cardio-pulmonary bypass. To establish cardio-pulmonary bypass a cannula is placed in the right atrial appendage. This cannula transports deoxygenated venous blood to the bypass machine where oxygenation takes place. A further cannula is placed in the ascending aorta in order to return oxygenated blood to the patient's systemic circulation (Hudak *et al.* 1990).

Determination of any microbial contamination present on the distal tip and the distal segment of the CVC was carried out by direct sampling. Immediately prior to the

cannulation of the right atrium the operating surgeon identified the distal segment of the CVC within the right atrium. This was carried out by the surgeon inserting a gloved finger into the atrium through the opening made in the atrial appendage. The distal segment of the CVC was then withdrawn through the atrial appendage and sampled by passing the catheter between a folded cellulose acetate membrane (Gelman Sciences, Ann Arbor, USA). (Figure 2-1 & 2-2). The CVC distal tip was also imprinted onto the membrane. The membrane was placed onto a 7% blood agar plate, which was incubated for 24h at 37°C in 5% CO_2 and then assessed for any microbial growth. Microorganisms were identified by standard microbiological techniques. Any plates without microbial growth were re-incubated for up to 96h. Immediately after direct sampling of the CVC the device was withdrawn by approximately 3cm at the skin insertion site. By withdrawing the catheter the distal segment of the device was repositioned within the right atrium.

Figure 2-1   Identification of the CVC distal tip within the right atrium

Figure 2-2 Sampling of the CVC distal tip whilst *in situ*. The CVC distal tip was passed through a folded cellulose acetate membrane

2.2.5 Identification of microorganisms on the operating surgeon's glove

Just prior to the operating surgeon identifying the distal segment of the CVC within the atrium, a swab of the surgeon's gloved finger was taken. A sterile cotton swab was applied 5 times to the whole gloved finger. The swab was then placed in 2ml of STM. Any microorganisms present on the swab were determined by the method described previously.

2.2.6 Determination of microbial contamination of the internal lumen of the CVC during insertion

A 10ml sample of blood was aspirated through the distal lumen of the CVC and placed into a blood culture bottle (Signal, Oxoid, Basingstoke, UK). This sample was used to detect any microorganisms which may have been transferred to the lumen of the CVC during the insertion procedure. To establish if any microorganisms were present in the stopcock entry port a swab of the port was taken prior to blood aspiration. A cotton swab moistened in Triton X-100 (0.1%) was placed in the entry port and rotated 180°, 10 times. The swab was then placed in 2ml of STM and the number of microorganisms contaminating the swab was determined as described above. A further 10 ml sample of blood was aspirated from a peripheral vein immediately post-operatively and placed in a blood culture bottle. The blood cultures were incubated for up to 7 days at 37°C in air. All blood cultures were subcultured on day 7 or when they signalled the presence of microbial growth.

2.2.7 Monitoring of infection

All patients were monitored daily for symptoms and signs of both local and systemic infection associated with the CVC. These included; erythema, oedema, suppurative phlebitis, cellulitis, abscess formation and exudate at the site of CVC insertion. The patients' core temperatures were also recorded. Any patients with evidence of systemic infection including; pyrexia following flushing of CVC, pyrexia unresponsive to broad spectrum antibiotics, pyrexia with no other obvious source of infection or evidence of localised CVC associated infection had blood for culture taken.

2.2.8 Determination of the number of microorganisms present on the CVC distal tip following removal

All catheters were removed from the patient by strict aseptic technique. Prior to CVC removal the skin insertion site was cleaned with a sterile gauze soaked in sterile normal saline. The insertion site was then sprayed with 70% aqueous isopropanol which was allowed to air dry for at least 2 minutes. The CVC was carefully explanted by applying gentle pressure to the proximal end of the device. On removal the 5cm distal segment of the CVC was cut with sterile scissors and placed in a sterile universal container. To determine the number of microorganisms present on the external surface of the CVC distal segment the roll plate method was used (Maki *et al.* 1977). Each 5cm length of catheter was rolled 5 times across the surface of a 7% blood agar plate. Microbial contamination of the internal surface of the CVC distal segment was determined by flushing the distal lumen with 1ml of STM, this process was repeated 5 times. A 100 μl aliquot of the STM solution was then plated onto a 7% blood agar plate. All the plates were incubated for 24h at 37°C in 5% CO_2. The plates were then assessed for microbial growth. Microorganisms were identified by standard microbiological techniques. Plates without microbial growth were re-incubated for up to 96 h.

2.3   Results

Thirty patients were recruited into the study, 21 male and 9 female, with a mean age of 60 years (range 31-80). The catheters were inserted into either the right internal jugular vein (27), the left internal jugular vein (1), or the right subclavian vein (2). The mean length of time that the CVC were *in situ* was 3 days (range 1-10). The type of cardiac surgery subsequently carried out on the patients is shown below (Table 2-1):

Table 2-1   **Type of cardiac surgery carried out on study patients**

TYPE OF OPERATION	NUMBER OF PATIENTS
Coronary Artery By-pass Grafting	20
Mitral Valve Replacement	2
Aortic Valve Replacement	6
Aortic Valve Replacement and Coronary Artery By-pass Grafting	2

The CVC sampled were not all inserted by the same anaesthetist, and were not all sampled *in situ* by the same surgeon.

2.3.1 Microbial contamination of CVC insertion equipment

Equipment associated with the insertion of the CVC was received from all thirty patients. The microbial contamination rate and the microorganisms isolated from each component of the insertion equipment are shown in Table 2-2.

2.3.1.1 *Insertion needle and cannula*

The insertion cannula and needle contaminated with diphtheroid bacilli had 2 morphologically distinct strains of the microorganism present.

2.3.1.2 *Guidewires*

The numbers of morphologically different CNS strains isolated from 11 guidewires are shown below in Table 2-3. One guidewire had 1 strain of CNS and 1 *Enterococcus* spp. The guidewire contaminated with diphtheroid bacilli had 2 morphologically different strains of the microorganism present.

2.3.1.3 *Dilators*

Of the CNS isolated from 12 dilators, 7 dilators had a single strain isolated, 3 had 2 morphologically distinct strains, 1 had 5 morphologically distinct strains and 1 a *Micrococcus* spp. and the remaining dilator had 1 strain CNS and 1 *Enterococcus* spp. The dilator contaminated with diphtheroid bacilli had 2 morphologically distinct strains of the microorganism present

Table 2-2   Microbial contamination of CVC insertion equipment

Insertion Equipment	Number Used	Number Contaminated (%)	Microorganisms Isolated
Insertion Cannula and Needle*	10	2 (20)	Enterococcus species 1 Diphtheroid bacilli 1
Insertion Needle*	20	7 (35)	Coagulase negative staphylococcus (CNS) 7
Guidewire	30	15 (50)	CNS 12 *Staphylococcus aureus* 2 Diphtheroid bacilli 1
Dilator	29	14 (48)	CNS 13 Diphtheroid bacilli 1
Scalpel	14	2 (14)	CNS 2

*Some operators used a combination of plastic insertion cannula with a needle; others used a needle alone for the initial skin puncture.

Table 2-3   Coagulase negative staphylococcus contamination of guidewires

CNS Number of Strains	Number of Guidewires
1	6
2	2
3	2
4	1

2.3.2 Microbial contamination of the skin around the CVC insertion site

All 30 patients had their CVC skin insertion site sampled after the catheter was inserted. Microorganisms were isolated from 20/30 (66%) of the patients. The microorganisms isolated were predominately CNS (19). One patient had diphtheroid bacilli. From the 20 patients from whom microorganisms were isolated at least forty two morphologically distinct strains of CNS were isolated and 2 strains of diphtheroid bacilli. The mean number of microorganisms isolated from the skin insertion site of the 20 patients was 1247 (range of 10 - 5320).

2.3.3 Isolation of microorganisms from CVC distal segment sampled *in situ*

Microorganisms were isolated from 5/30 (17%) CVC distal segments sampled *in situ*. Sampling took place within 1 h of catheter insertion. All microorganisms were CNS: *S. epidermidis* (4) and *S. cohnii* (1). The mean number of cfu isolated was 4 ± 3 (mean $\pm$ SD). Two of the isolates were slime positive, both *S. epidermidis*, and 3 were slime negative. Identification of the CNS by the API staph system was performed on the isolates recovered from the CVC distal tip segments sampled *in situ*. These profiles were compared to the profiles of microorganisms recovered from the equipment used to insert the 5 catheters positive *in situ*. The microorganisms isolated along with their antibiotic sensitivities are shown in Table 2-4

The microorganisms isolated from 4/5 of the CVC distal tips were dissimilar to those isolated from the CVC insertion equipment or the skin insertion site. All isolates were sensitive to the skin disinfectant that was used to prepare the skin insertion site prior to cannulation (chlorhexidine gluconate 2.5% in IMS). All 5 patients with positive CVC distal segments, when sampled whilst *in situ*, were given flucloxacillin 1g and cefuroxime 1.5 g on induction of anaesthesia. Of the CNS isolated from the 5 patients 3/5 (60%) were sensitive to methicillin. (2 *S. epidermidis* and 1 *S. cohnii*).

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Antibiotic Sensitivities

Pt No	Source of Organism	Organism Isolated	Penicillin	Vancomycin	Rifampicin	Erythromycin	Fusidic Acid	Gentamicin	Methicillin
1	Guidewire	*S. aureus*	R	S	S	R	R	S	S
	Filter	*S. epidermidis*	S	S	S	S	S	S	S
2	Guidewire	*S. aureus*	R	S	S	S	S	S	S
	Skin	*S. hominis*	R	S	S	S	S	S	S
	Scalpel	*S. warneri*	R	S	S	S	R	S	S
	Filter	*S. epidermidis*	R	S	S	R	S	R	R
3	Guidewire 1	*S. epidermidis*	S	S	S	S	S	S	S
	Guidewire 2	*S. epidermidis*	R	S	S	S	S	S	S
	Guidewire 3	No ID*	S	S	S	S	S	S	S
	Dilator	*S. epidermidis*	R	S	R	R	R	R	R
	Skin 1	*S. epidermidis*	S	S	S	S	S	S	S
	Skin 2	*S. epidermidis*	S	S	S	S	S	S	S
	Filter	*S. epidermidis*	R	S	S	S	S	R	R
4	Guidewire 1	Low discrimination*	S	S	S	S	S	S	S
	Guidewire 2	Low discrimination*	S	S	S	S	S	S	S
	Guidewire 3	*S. epidermidis*	S	S	S	S	S	S	S
	Dilator 1	Low discrimination*	S	S	S	S	S	S	S
	Dilator 2	*S. epidermidis*	S	S	S	S	S	S	S
	Skin 1	*S. epidermidis*	S	S	S	S	S	S	S
	Skin 2	*S. epidermidis*	S	S	S	S	S	S	S
	Filter	*S. epidermidis*	S	S	S	S	S	S	S
5	Skin	*S. schleiferi*	R	S	S	S	S	S	S
	Filter	*S. cohnii*	R	S	R	S	S	S	S

Table 2-4 Microorganisms isolated from both the CVC whilst *in situ* and the associated insertion equipment. Antibiotic patterns are also displayed. (* Isolates were not identified by the API Staph System.)

2.3.4 Isolation of microorganisms from the surgeon's glove

The microbiology of the surgeon's glove was determined in 6 cases (20%). All the samples were sterile. One of the gloves tested was from a surgeon who sampled the distal portion of a CVC from which microorganisms were isolated. Each filter used to sample the CVC *in situ* was handled by the operating surgeon, none of the filters showed evidence of microbial contamination from this source.

2.3.5 Microbial contamination of the CVC internal lumen

2.3.5.1 *Isolation of microorganisms from the CVC hub and blood cultures*

Thirty patients had hub swabs and blood cultures taken through the CVC immediately after the distal tip was sampled *in situ*. The hub swabs and blood cultures were negative in all cases. Blood for culture was obtained from a peripheral vein in 27/30 patients (90%). All cultures were negative. Three patients died during surgery and therefore peripheral samples were not obtained.

2.3.6 Microbial colonisation of the CVC distal segment following removal

2.3.6.1 *Distal segment external surface*

Twenty seven (90%) of the CVC distal segments following removal were received in the laboratory for analysis. Three out of 27 (11%) tips had $\geq$ 15 cfu recovered from the external surface. One catheter distal segment was colonised with *P. aeruginosa*, this microorganism was isolated from a patient with CNS impacted on to the CVC distal segment on insertion. The number of cfu and the organisms isolated are shown in Table 2-5.

2.3.6.2 *Distal segment internal surface*

Of the 27 CVC distal segments received for analysis, 1 was colonised (4%) with $\geq$ 15 cfu on the internal surface, 70 cfu of CNS were isolated. There was no external colonisation from this patient's CVC distal segment.

2.3.7 Evidence of CVC-associated infection

2.3.7.1 *Systemic infection*

Of the 30 patients studied none had evidence of systemic infection. Blood cultures were taken from 2 patients in the post-operative period, however both were negative.

2.3.7.2 *Local infection*

Symptoms and signs of localised CVC infection were reported in 7 patients (23%). Erythema was present at the CVC skin insertion site of 5 patients (16%), oedema and erythema in 1 patient (3%) and the 1(3%) patient had evidence of both erythema and cellulitis.

Table 2-5   **Microbial colonisation of the CVC distal segment external surface following removal**

NUMBER OF CFU ISOLATED	MICROORGANISM
69	CNS
103	CNS
31	*P. aeruginosa*

2.4   Discussion

This study has demonstrated that, despite the use of aseptic techniques, including thorough and appropriate skin preparation and antibiotic prophylaxis, CVC can become contaminated with microorganisms on insertion through the skin. The components of the CVC insertion sets were also contaminated during the insertion procedure. The most likely source of contamination was the patients skin. Skin microorganisms may have been transferred from the skin surface, onto the surface of the components of the insertion equipment. The distal segment of the CVC may also have become contaminated by this route. This is of particular importance as it is from the distal tip of the catheter that the majority of CVC related infections are thought to arise. It was demonstrated that microorganisms were not only present at the CVC insertion site after disinfection, but also within the dermal layers. This was evident as microorganisms were not recovered from the skin surface in 6% of patients but were recovered from the equipment used to place the CVC. As microorganisms were not present on the skin surface after cleaning, this region could not be identified as the source of contamination of insertion equipment. However it is likely that the dermal layers of the skin were the source of contamination in these patients.

Coagulase negative staphylococci were the predominant microorganisms identified from the CVC distal segment sampled whilst *in situ*, however the exact origin of the microorganism was not conclusively identified in this study. The use of the API staph system and antibiograms did not assist further with the identification of the source of the microorganisms. This may have reflected the relatively large numbers of morphologically distinct colonies isolated from the skin insertion site, many of which had different API profiles and antibiograms. Due to the large variations in colonial types and the numbers of potentially different species involved no further typing of microorganisms was attempted at this stage. However further typing of selected isolates from the skin, insertion equipment and CVC distal tip was conducted by Dr Livesley at Aston University (Birmingham) using pulsed-field gel electrophoresis (Appendix 1).

Of the 5 catheter distal segments from which CNS were recovered *in situ*, 3 were sensitive to methicillin. This suggests that prophylactic antibiotics may not prevent this potential route of catheter contamination. Bock *et al.* (1990) reported a reduction in CRS when oxacillin was used prophylactically immediately prior to central venous cannulation. However, McKee *et al.* (1985) and Ranson *et al.* (1990) reported the incidence of catheter related bacteraemia was not reduced when vancomycin was used. The timing of prophylactic antibiotic administration prior to interventional procedures needs to be considered. If prophylactic antibiotics were administered at a specific time interval prior to an interventional procedure and not immediately proceeding it, their action may be more effective. More controlled studies are required in this area.

Of the CVC distal tips examined on removal 3 out of 27 (11%) had >15 cfu recovered from their external surface. The patients from whom the catheters were explanted however did not exhibit any symptoms or signs of systemic infection. These results question the roll plate method (Maki *et al.* 1977) which is used widely to microbiologically analyse CVC distal tips. Maki *et al.* (1977) suggest that a colony count of ≥ 15 cfu is indicative of infection whereas a lower colony count represents colonisation. The roll plate method, in this study, did not prove to be a good indicator of catheter-related infection. These findings highlight the need for microbiological results of CVC distal tip analysis to be interpreted only with direct reference to the patient's clinical condition.

None of the patients studied developed clinical evidence of CVC-related infection. This may have been due to two factors. Firstly, the catheters remained in place for a relatively short period of time (mean 3 days). It is well recognised that there is a strong association between prolonged central venous cannulation and an increased risk of catheter contamination and bacteraemia (Hampton and Sheretz, 1988., Henderson, 1988., Elliott, 1993). Secondly, sampling the CVC whilst *in situ*, by passing the distal portion of the device through a folded cellulose acetate membrane, may, in the 5 positive catheters sampled, have removed viable microorganisms that could have potentially been the nidus of a CRS.

This work has demonstrated that the skin is a major source of microorganisms even after skin disinfection. This finding not only has implications for the management of CVC but also for other invasive devices which are inserted through the skin in a similar manner to the Seldinger technique. This includes the placement of vascular stents and vena cava filters. Microorganisms become impacted onto the surface of devices as they pass through the skin to become a subsequent nidus of infection. New methods to combat these potential routes of infection need to be considered. These may include the development of more effective skin disinfecting agents which not only act on the skin surface but also penetrate to the skin's deeper layers. Alternative approaches to device insertion may also be adopted. These may include methods whereby the device being inserted does not come into contact with the skin, thereby eliminating this potential source of contamination.

3. Determination of whether CVC become contaminated with microorganisms on insertion when inserted through a swan sheath.

3.1 Introduction

It was demonstrated in chapter 2 that CVC can be contaminated with microorganisms during the insertion of the device through the skin. The components of the CVC insertion sets may also become contaminated during the insertion procedure. Microbial contamination of the CVC and its associated insertion equipment occurred despite the use of aseptic techniques, thorough and appropriate skin disinfection and prophylactic antimicrobial therapy. The skin was the most likely source of microbial contamination.

The object of this part of the study was to determine whether, by avoiding contact with the skin during the insertion procedure, microbial contamination of CVC can be prevented.

3.2 Materials and Methods

Thirty patients undergoing coronary artery bypass grafting or cardiac valve replacement procedures were recruited into the study following informed consent. These patients were due to receive a CVC as part of their medical treatment. In addition to a CVC the patients also received a swan sheath. After insertion of the swan sheath and CVC the associated insertion equipment was examined for the presence of microorganisms. The CVC were assessed whilst *in situ* for microbial contamination.

3.2.1 Swan sheath and CVC insertion

A full aseptic technique was employed by the medical staff during the swan sheath and CVC-insertion procedure. The proposed swan sheath skin insertion site and surrounding area was sprayed with chlorhexidine gluconate 2.5% in IMS (DuPuy Healthcare, Leeds, UK), and allowed to dry for 2 minutes. Sterile drapes were then placed around the proposed skin insertion site and non-clean areas. All sheaths were inserted by a Seldinger technique (Soni, 1996). The swan sheaths were 10 cm, 8.5 Fr polyurethane manufactured by either Argon Medicals, Athens, Texas, USA or Baxter Healthcare Corporation, Illinois, USA. After swan sheath insertion the CVC was introduced through the lumen of the sheath (Figure 3-1). The CVC were introduced to a depth of between 25 and 30cm, into the right atrium. This depth was selected to allow the distal portion of the CVC to be sampled during surgery. All CVC were polyurethane triple lumen, 30cm, 7 Fr, (Deltacath®, Becton Dickinson, Meylan, France). By inserting the CVC through the swan sheath, the CVC avoided contact with the skin.

3.2.2 Determination of microbial contamination of the swan sheath insertion equipment.

The components of the swan sheath insertion set including the introducer needle/cannula, guidewire, dilator and scalpel, were collected after use in a sterile container and assessed for microbial contamination as described in section 2.2.2.

3.2.3 Evaluation of the number of microorganisms on the skin at the swan sheath insertion site

Immediately following placement of the swan sheath the 2cm^2 area of skin surrounding the catheter insertion site was swabbed to determine the number of microorganisms remaining on the surface of the skin. All swabs were obtained and processed as described in section 2.2.3.

3.2.4 Sampling of the CVC distal tip whilst *in situ*

Determination of microbial contamination present on the distal tip and the distal segment of the CVC was carried out by direct sampling as described as described in section 2.2.4. After sampling the cellulose acetate membrane was placed onto a 7% blood agar plate which was incubated for 24 h at 37°C in 5% CO_2. Microorganisms were identified by standard microbiological techniques. Any plates without microbial growth were re-incubated. The sterility of the filters was confirmed by standard microbiological techniques.

3.2.5 Identification of microorganisms on the operating surgeon's glove

Just prior to the operating surgeon identifying the distal segment of the CVC within the atrium, a swab of the surgeon's gloved finger was taken. A sterile cotton swab was applied 5 times to the whole gloved finger. The swab was then placed in 2ml of STM. Any organisms present on the swab were determined as described previously.

3.2.6 Determination of microbial contamination of the internal lumen of the CVC during insertion

A 10ml sample of blood was aspirated through the distal lumen of the CVC and placed into a blood culture bottle (Signal, Oxoid, Basingstoke, UK). This sample was used to detect any microorganisms which may have been transferred to the lumen of the CVC during the insertion procedure. To establish if any microorganisms were present in the stopcock entry port a swab of the port was taken prior to blood aspiration, as described previously. A further 10 ml sample of blood was aspirated from a peripheral vein immediately post-operatively and placed in a blood culture bottle. The blood cultures were incubated for up to 7 days at 37°C in air. All blood cultures were subcultured on day 7 or when they signalled the presence of microbial growth.

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3.2.7 Monitoring of infection

All patients were monitored daily for symptoms and signs of both local and systemic infection associated with the CVC, as described earlier. Any patients with evidence of systemic infection had blood for culture taken.

3.2.8 Removal of catheters

3.2.8.1 *CVC removal*

All the CVC were removed by strict aseptic technique. Prior to removal of the CVC the swan sheath entry port was cleaned with sterile gauze soaked in sterile normal saline. The swan sheath entry port was then sprayed with 70% isopropanol. The isopropanol was allowed to air dry for at least 2 minutes. The CVC was then withdrawn through the swan sheath by applying gentle pressure to the proximal end of the CVC. On removal the 5cm distal segment of the CVC was cut with sterile scissors and placed in a sterile universal container.

3.2.8.2 *Swan sheath removal*

Following removal of the CVC the swan sheath skin insertion site was cleaned with sterile gauze soaked in sterile normal saline. The skin insertion site was then sprayed with 70% isopropanol. The isopropanol was allowed to dry air dry for at least 2 minutes. The swan sheath was then withdrawn by applying gentle traction to the proximal end of the catheter. On removal the 5cm distal segment of the swan sheath was cut with sterile scissors and placed in a sterile universal container.

3.2.9 Determination of the number of microorganisms present on the swan sheath and CVC distal tips following removal

The internal and external surfaces of both the swan sheaths and CVC distal segments were examined for microbial colonisation on removal. To determine the number of microorganisms present on the external surface of the catheters distal segments the roll plate method was used (Maki *et al.* 1977). Microbial contamination of the internal surface of the swan sheath distal segment was determined by flushing the lumen with 1ml

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of STM, this process was repeated 5 times. A 100 μl aliquot of the STM solution was then plated onto a 7% blood agar plate. These processes were repeated for the CVC distal segments. All the plates were processed as described previously.

Figure 3-1   **A triple lumen central venous catheter inserted *via* a swan sheath**
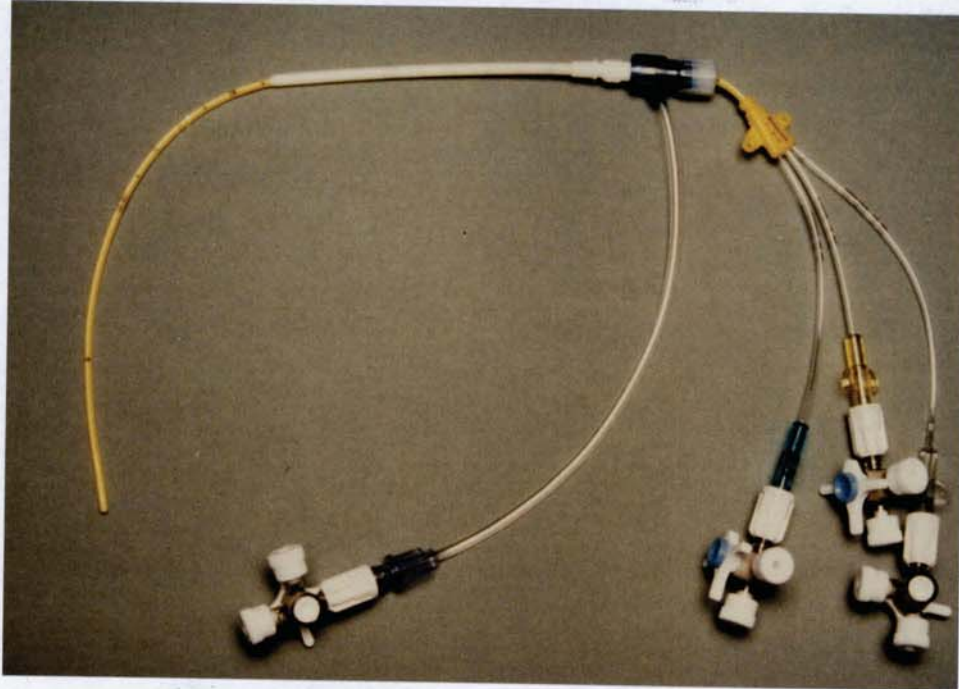
3.3 Results

Thirty patients were recruited into the study, 22 male and 8 female, with a mean age of 62 years (range 42-75). Twenty nine patients had the catheters inserted *via* the right internal jugular and 1 patient underwent right subclavian vein catheterisation. The mean length of time the catheters were *in situ* was 3 days (range 1-8). The type of surgery subsequently carried out on the patients is shown in Table 3-1.

3.3.1 Microbial contamination of the swan sheath insertion equipment

Equipment associated with the insertion of the swan sheath and CVC was received from all thirty patients. Microbial contamination of the swan sheath and CVC insertion equipment is shown in Table 3-2.

3.3.1.1 *Insertion cannula and needle*

Of the CNS isolated from the 2 insertion cannulae and needles, 1 had 2 morphologically distinct strains and 1 had 1 strain CNS and 1 *S. aureus*

3.3.1.2 *Insertion needle*

Of the CNS isolated from the 2 insertion needles 1 was single strain and 1 had 2 morphologically distinct strains. The *S. aureus* isolated was a single strain.

3.3.1.3 *Guidewires*

From the 11 guidewires contaminated with CNS, 4 were single strain, 5 had 2 morphologically distinct strains, 1 had 1 strain CNS and 1 *S. aureus*, 1 had 2 strains of CNS, 1 diphtheroid bacillus and 1 *Streptococcus sanguis*. One guidewire was contaminated with *S. aureus* which was a single strain.

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3.3.1.4 *Swan sheath introducer*

Of the CNS isolated from 8 swan sheath introducers 5 were single strain, 2 had 2 morphologically distinct strains, 1 had 2 morphologically distinct strains, 2 strains of diphtheroid bacilli and *Streptococcus sanguis*. Of the *S. aureus* isolated 1 was single strain and 1 was 1 strain *S. aureus* and 1 CNS. The diphtheroid bacilli isolated was a single strain.

Table 3-1   **Type of cardiac surgery carried out on study patients**

TYPE OF OPERATION	NUMBER OF PATIENTS
Coronary Artery By-pass Grafting	28
Aortic Valve Replacement	1
Aortic Valve Replacement and Coronary Artery By- pass Grafting	1

The CVC sampled were not all inserted by the same anaesthetist, and were not all sampled *in situ* by the same surgeon.

Table 3-2   Microbial contamination of swan sheath and CVC insertion equipment

Insertion Equipment	Number Used	Number Contaminated (%)	Microorganisms Isolated
Insertion Cannula and Needle**	14	2 (14)	CNS 2
Insertion Needle**	16	3 (19)	CNS 1 *Staphylococcus aureus* 1
Guidewire	30	12 (40)	CNS 11 *Staphylococcus aureus* 1
CVC Dilator*	16	5 (31)	CNS 5
Swan Sheath Introducer	30	11 (37)	CNS 8 *Staphylococcus aureus* 2 Diphtheroid bacilli 1
Scalpel	30	7 (23)	CNS 6 *Staphylococcus aureus* 1

*Some operators used a CVC dilator prior to using the swan sheath introducer.

**Some operators used a combination of plastic insertion cannula with a needle. others used a needle alone for the initial skin puncture.

3.3.2 Determination of microbial contamination of the skin around the swan sheath insertion site

All 30 patients had their swan sheath skin insertion sites sampled immediately after the device was inserted. Microorganisms were isolated from 23/30 patients (76%). The microorganisms isolated are shown in the Table 3-3. From the swan sheath skin insertion sites 42 morphologically distinct strains of CNS were isolated. The mean number of organisms isolated from 23 patients was 1634 (range of 40 - 7520).

Table 3-3   Microorganisms isolated from around the swan sheath skin insertion sites

Microorganism Isolated	Number of Patients
CNS	19
CNS and *Staphylococcus aureus*	1
CNS and *Streptococcus sanguis*	1
CNS and *Bacillus* spp.	1
Diphtheroid bacilli	1

3.3.3 Isolation of microorganisms from the CVC distal segment sampled *in situ*

Microorganisms were isolated from 1/30 (3%) CVC distal segments sampled whilst *in situ*. Sampling took place within 1 h of the catheters being inserted. From the positive CVC distal segment 1 cfu of CNS was isolated, the organism was identified as *Staphylococcus capitis*. *Staphylococcus capitis* was also isolated from the patients skin swab, however the API profile was not the same as the strain isolated from the CVC distal segment when sampled *in situ* (Table 3-4). The CNS isolated from the catheter distal segment was slime negative. The isolate was sensitive to the skin disinfectant used to prepare the skin insertion site prior to cannulation (chlorhexidine gluconate 2.5% in IMS), and also sensitive to methicillin. The patient received flucloxacillin 1g and cefuroxime 1.5g on induction of anaesthesia. *Staphylococcus aureus* was isolated from the guidewire, insertion needle, swan introducer and scalpel from this patient.

3.3.4 Isolation of microorganisms from the surgeon's glove

The surgeons gloves was sampled in all 30 cases. Twenty nine were negative (97%). *Enterococcus* spp (900 cfu) was isolated from one swab taken from a surgeon's gloved finger. The filter used by this surgeon to sample the CVC distal tip *in situ* had 1 cfu of CNS isolated from it. *Enterococcus* spp. was not isolated from this filter.

Table 3-4 Microorganisms isolated from both the CVC whilst *in situ* and the associated insertion equipment. Antibiotic sensitivities are also displayed.

SOURCE OF MICROORGANISM	MICROORGANISM	P	V	RF	E	F	G	M
Skin	*S. capitis*	S	S	S	S	S	S	S
Guidewire	*S. aureus*	R	S	R	S	S	S	R
Needle	*S. aureus*	R	S	R	S	S	S	R
Swan Introducer	*S. aureus*	R	S	R	S	S	S	R
Scalpel	*S. aureus*	R	S	R	S	S	S	R
Filter	*S. capitis*	S	S	S	S	S	S	S

Key
R   Resistant
S   Sensitive
P   Penicillin
V   Vancomycin
RF   Rifampicin
E   Erythromycin
F   Fusidic acid
G   Gentamicin
M   Methicillin

3.3.5 Microbial contamination of the CVC internal lumen

3.3.5.1 *Isolation of microorganisms from the CVC hub and blood cultures*

Thirty patients had hub swabs and blood for culture taken through their CVC immediately after the CVC distal tip was sampled *in situ*. The hub swabs and blood cultures were all negative. Blood for culture was obtained from a peripheral vein in 28/30 patients (93%), 1 patient had blood taken through the subclavian vein as peripheral access was poor. All cultures were negative.

3.3.6 Microbial colonisation of the swan sheath distal segment following removal

3.3.6.1 *External surface*

Twenty nine out of 30 (97%) swan sheath distal segments following removal were received in the laboratory for analysis. Two out of 29 (7%) of the swan sheaths had ≥ 15 cfu recovered from the external surface (100 and 50 cfu) of which all were CNS. Two out of 29 (7%) swan sheaths had < 15 cfu recovered from the external surface (5 cfu CNS and *S. aureus* and 6 cfu CNS).

3.3.6.2 *Internal Surface*

Of the 29 tips received for analysis 3 (10%) had organisms recovered from the internal surface. Coagulase negative staphylococcus was isolated from 2 tips (1020 and 400 cfu) and *S. aureus* and 2 morphologically distinct strains of CNS (220 cfu) from the remaining tip.

3.3.7 Microbial colonisation of CVC distal segments following removal

3.3.7.1 *External surface*

Thirty CVC distal segments following removal were received in the laboratory for analysis. Four out of 30 patients (13%) had ≥ 15 cfu recovered from the external surface of their CVC distal tip. The tip colonised with CNS, diphtheroid bacilli and *Streptococcus sanguis* was recovered from the patient whose CVC distal segment was contaminated *in*

situ. Two CVC had < 15 cfu recovered from the external surface, (2 and 10 cfu) of which all were CNS. The number of cfu and the microorganisms isolated are demonstrated in Table 3-5.

3.3.7.2 *Internal surface*
Two out of 30 (6%) of the CVC distal tips had microorganisms recovered from the internal surface (800 cfu CNS and 170 cfu CNS and diphtheroid bacilli).

3.3.8 Swan sheath internal colonisation and CVC external colonisation
Of the 6 CVC that were contaminated on the external surface the internal lumen of the swan sheath from where it was removed was contaminated in 3 cases. The numbers and types of microorganisms isolated are shown in Table 3-6.

3.3.9 Evidence of CVC-associated infection
3.3.9.1 *Systemic infection*
None of the patients studied had evidence of systemic infection. Blood for culture was not taken from any patient during the post-operative period.

3.3.9.2 *Local infection*
Erythema at the swan sheath insertion site was reported in 11 patients (37%). The erythema was not considered to be associated with local catheter-related infection in any of these patients.

Table 3-5   Microorganisms isolated from the CVC distal segment external
            surface following removal

NUMBER OF CFU ISOLATED	MICROORGANISM
≥ 500	CNS
250	CNS
40	CNS and Diphtheroid bacilli
18	CNS, Diphtheroid bacilli and *Streptococcus sanguis*

Table 3-6   Microorganisms isolated from both the CVC external surface and the
            swan sheath internal surface.

CVC EXTERNAL SURFACE (cfu)	ORGANISM ISOLATED	SWAN SHEATH INTERNAL SURFACE (cfu)	ORGANISM ISOLATED
> 500	CNS	1020	CNS
250	CNS	400	CNS
2	CNS	220	CNS

3.4 Discussion

Central venous catheters, when inserted by the Seldinger technique, become contaminated with microorganisms as the device passes through the skin, despite the application of aseptic technique including thorough skin cleaning with an appropriate skin disinfectant (chapter 2). The most likely source of this microbial contamination is the patient's skin flora. The aim of this study was to determine if, by avoiding contact with the skin, the incidence of CVC microbial contamination could be reduced. It was demonstrated that by inserting CVC *via* a protective sheath, for example a swan sheath, the incidence of catheter contamination at the early stages of catheterisation was reduced. Microbial contamination of the CVC distal tips when the catheters were inserted directly through the skin was 17% (5/30), in comparison to 3% (1/30) when CVC were inserted *via* a swan sheath. Although a reduction in microbial contamination was shown, due to the relatively small sample size a significant difference between the two groups was not achieved ($p = >0.05$ Chi square test).

A single colony of CNS was isolated from one catheter distal tip only, when sampled *in situ* after being introduced through a swan sheath. The microorganism may have become impacted onto the swan sheath during the insertion procedure which in turn could have contaminated the distal tip of the CVC during the insertion procedure.

The microorganism isolated from the CVC distal tip *in situ* was *S. capitis*. This microorganism was also isolated the patient's swan sheath skin insertion site. Pulsed field gel electrophoresis was conducted (Dr Livesley at Aston University Birmingham) on the isolates and this technique demonstrated that the isolates were closely related genotypically.

At the time of catheter removal ≥ 15 cfu were isolated from the external surface of 4 out 30 CVC distal tips which had been inserted through a swan sheath. This was similar to the previous study where CVC were inserted directly through the skin with 3 out of 27 distal tips having ≥ 15 cfu present on their external surface (section 2.3.6.1). It would appear that the presence of a swan sheath did not prevent colonisation of the CVC

external surface once the device was in place. Extraluminal migration of microorganisms from the patient's skin surface to the CVC distal tip is an unlikely mechanism for this microbial contamination as the CVC was not in direct contact with the skin.

Studies conducted on pulmonary artery flotation catheters (PA), which are used to measure left heart function, and are inserted *via* swan sheaths to protect the balloon tip of the device during the insertion procedure have an associated infection rate of between 14% and 28% (Martin *et al.* 1989., Smith *et al*, 1991., Pittet *et al.* 1994). It has been reported that the major source of PA catheter-associated infection is the introducer sheath as it provides a throughway for microorganisms (Mermel and Maki, 1997) which is in agreement with current findings.

On removal of the study catheters 2 swan sheaths and 4 CVC had ≥ 15 cfu isolated from their external distal surface. The patients who had these catheters in place did not exhibit any symptoms or signs of systemic infection. The current findings also demonstrate the need for catheter tip microbiology results obtained by the roll plate method to be interpreted in the light of the patient's clinical condition. The roll plate method in this study was a poor indicator of CRS.

It is well recognised that for both CVC and for PA catheters the incidence of CRS increases with the duration of catheterisation. The mean duration of catheterisation in the current study was 3 days. This relatively short period of catheterisation may therefore account for there being no evidence of CRS in the patients studied.

The *S. capitis* isolated from the CVC whilst *in situ* was sensitive to methicillin. The patient had received prophylactic antibiotics which included flucloxacillin immediately prior to catheter insertion. As the previous study suggested this highlights the need for further work to be conducted into the timing and efficacy of prophylactic antibiotics. Indeed the administration of broad spectrum antimicrobials immediately prior to central venous catheterisation may not completely prevent the development of the early catheter colonisation.

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This study has demonstrated that there is a reduction in the incidence of microbial contamination when CVC are inserted *via* a sheath as opposed to being inserted directly through the skin. The likely reason for the reduction in contamination is that microorganisms are not impacted onto the distal tip of the CVC during the insertion procedure. The study has also demonstrated that by inserting CVC through swan sheaths the incidence of catheter colonisation at the time of device removal is not reduced. This suggests that when a CVC is *in situ* the sheath does not offer any additional protection from microbial colonisation.

4. Determination of the potential for central venous catheter microbial contamination from a needleless connector

4.1 Introduction

Needleless connectors for use with intravascular catheters have been introduced into clinical practice. Traditionally, the majority of IV connections have been made by either by luer:luer lock or by a needle penetrating a latex seal (Figure 4-1). Needleless connectors comprise of a male connection which attaches onto the luer of intravascular devices. These connectors are self sealing and do not require any additional protective cover. Access to the intravascular device is achieved by depressing the silicone or latex seal with a luer slip connection, either a intravenous fluid administration set or a syringe tip.

There are 3 advantages associated with the use of needleless devices:

a) To prevent needlestick injury

b) To overcome the problem of luer ports being inadvertently left open

c) To facilitate aseptic technique

(Brown *et al.* 1997)

It has further been demonstrated that needleless devices, when used correctly, not only reduce the number of needlestick injuries but the associated savings balance their acquisition costs (Yassi *et al.* 1995). However, it is unclear whether or not these devices may act as a portal of entry for microorganisms to central venous catheters. It has previously been reported that microorganisms gain access to CVC by the external route, from the skin insertion site along the outside of the device, or by the internal route, *via* luer connectors (Elliott and Faroqui, 1993). It has also been demonstrated that colonisation of stopcocks and catheter hubs is an important factor in the development of CRS (Sitges- Serra *et al.* 1984, Mermel *et al.* 1991). Microorganisms from this source may pass along the internal lumen of a CVC resulting in sepsis. Tebbs *et al.* (1996) reported that up to 23% of entry ports were contaminated with microorganisms during

use and this may therefore be an important source of sepsis. In comparison there have been limited numbers of reports on the potential of needleless connectors as a source of CRS. Chodoff *et al.* (1995) raised concerns regarding patient safety when such devices were used. It was reported that seven cases of Gram negative bacteraemia occurred when a needleless dispensing pin was used to withdraw 0.9% saline. The authors suggested that although needleless devices may protect employees from needlestick injuries they may pose a threat to patient health. Indeed, Danzig *et al.* (1995) reported an increase in septicaemia associated with needleless devices in patients who were receiving home infusion therapy. Conversely, Adams *et al.* (1993) demonstrated that there was no increased risk of CRS when needleless devices were used with appropriate aseptic technique.

The aim of this part of the study was to further address the potential infection risk of needleless connectors. A newly introduced needleless device, the Connecta Clave® was evaluated. The device was assessed for:

a) The potential for microorganisms to pass through once challenged with a microbial load
b) The potential for microbial contamination in clinical practice
c) The effectiveness of different methods of disinfection

The results from each assessment will be discussed after the associated methodology.

Figure 4-1   Traditional IV connectors
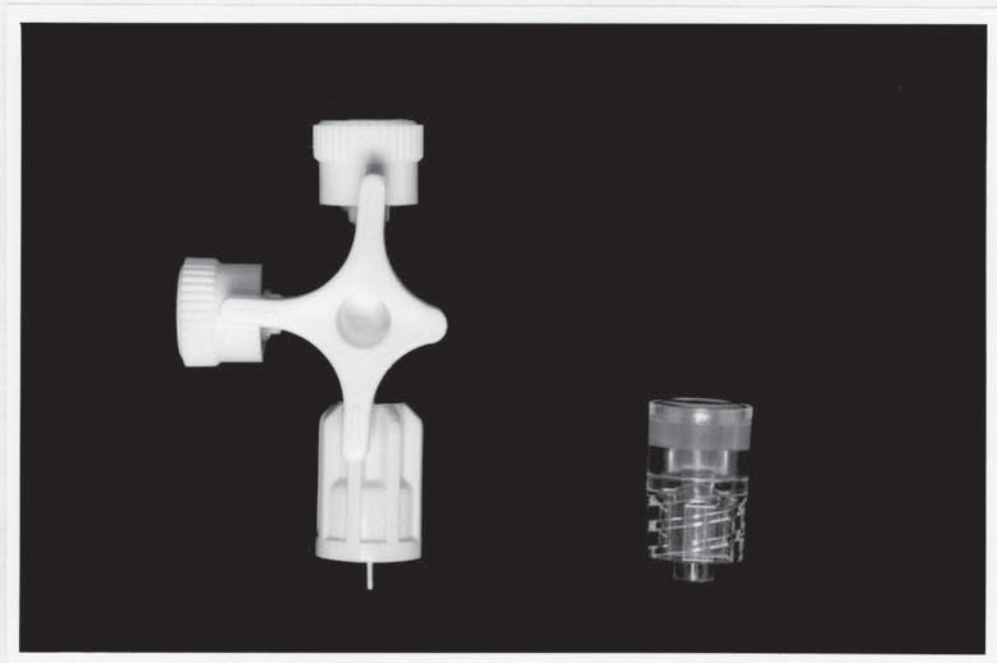
Left: Three-way tap
Right: Latex needle access device

4.2 Materials

4.2.1 The needleless connector - Connecta Clave®

The needleless connector (Figure 4-2) consists of a silicone compression seal (Figure 4-3) onto which a syringe or male luer connector can be directly attached. By attaching a male connection the silicone seal is depressed and the internal piercing mechanism is activated (Figure 4-4/5), this then allows a direct fluid pathway through the connector. The device is specifically designed to ensure that when the fluid pathway is opened there is no contact between the external surfaces of the connector's compression seal and the fluid.

4.2.2 Disinfectants

- 70% isopropanol swabs (Steret®, Seton Healthcare, Oldham, UK)
- Chlorhexidine 2.5% v/v in 70% industrial methylated spirit (Hydrex DS Derma Spray, Depuy Healthcare, Leeds, UK)

4.2.3 Microbiology media

- Nutrient broth (Oxoid, Basingstoke, UK)
- Nutrient agar plates (nutrient broth containing 1% agar no 1 (Oxoid, Basingstoke, UK)

4.2.4 Microorganism

- *Staphylococcus epidermidis* - NCTC 9865

Figure 4-2   The needleless connector the Connecta Clave®, showing the outside surface with locking threads (upper) which allows luer connection and distal end for attachment to catheters

0

30 mm

Figure 4-3   The silicone compression seal of the Connects Clave®. The compression seal is located at the upper end of the device.
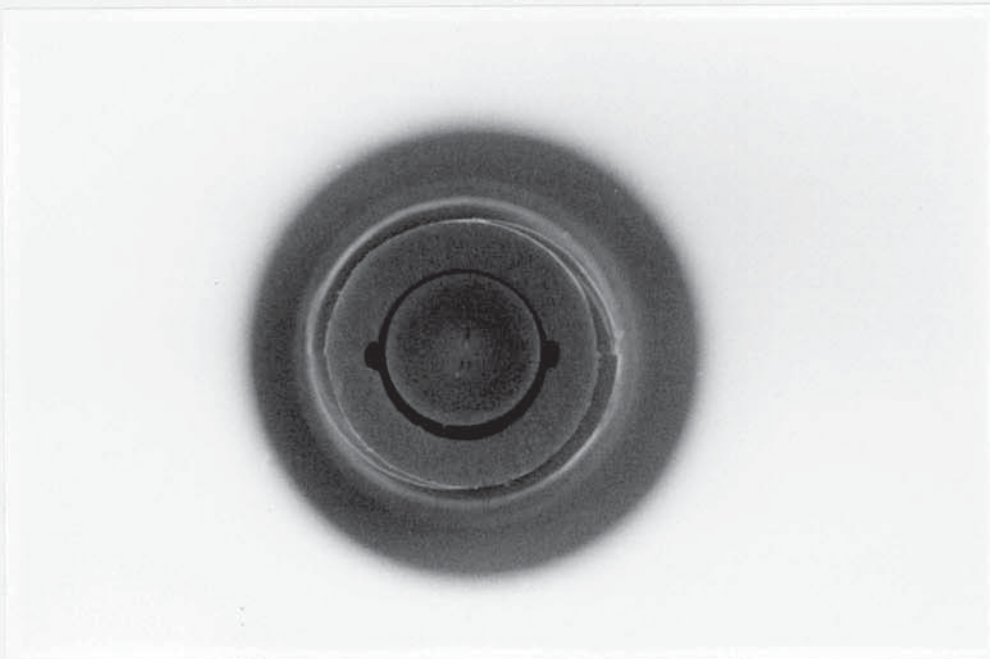
0

8 mm

Figure 4-4   Diagrammatic representation of the internal mechanism of the Connecta Clave®. The connector consists of a compression seal which is adherent to an internal piercing element.

Aston University

Illustration removed for copyright restrictions

Figure 4-5   Diagrammatic representation of the passage of fluid through a Connecta Clave®. The underlying piercing element penetrates the seal and allows the passage of fluid through the device, avoiding the external components.

Aston University

Illustration removed for copyright restrictions

4.3   Methods and Results

4.3.1   Assessment 1 - Microbial contamination of the needleless connectors

Sixty sterile needleless connectors were each subjected to 30 simulated clinical uses. Each simulated use involved attaching a sterile 10 ml syringe to every connector, injecting 1 ml of sterile normal saline through the device, as in clinical practice. After the 1 ml injection, the devices were disinfected with a 70% isopropanol swab (Steret®), which is the current recommended policy in the clinical situation at the Queen Elizabeth Hospital, Birmingham. A new Steret® was used for each activation. Each swab was firmly applied and rotated through 180° five times over the surface of the silicone surface and the associated rim of the device. The devices were then allowed to dry, in air, at 20°C over 2 minutes.

After the simulated uses, the 60 needleless connectors were inoculated with S. *epidermidis* (NCTC 9865). An overnight culture of *S. epidermidis* in nutrient broth was standardised to a concentration of 1×10^6 cfu/ml. This was achieved by measuring the optical density (OD) of the suspension at 570 nm and calculating the number of organisms with a standard curve of OD versus viable counts. The cultures were adjusted to the required concentration with fresh nutrient broth. Ten μl of bacterial suspension containing 1×10^4 cfu was then applied to the compression seal of each connector. The devices were placed at 37°C in air for 30 minutes to allow the bacterial suspension to dry. Fifty of the connectors were disinfected with isopropanol swabs, as described above. The remaining 10 connectors acted as controls and were not cleaned.

A sterile 5 ml syringe was then attached to every device and 5 ml of sterile normal saline passed through each. The first 1ml aliquot was collected and 10 μl inoculated onto the surface of a nutrient agar plate. Nine ml of nutrient broth was added to the remainder of the aliquot. The plates and broths were then incubated in air at 37°C and examined for growth after 48 h. *Staphylococcus epidermidis* (NCTC 9865) produces a red pigment when grown on nutrient agar plates and was identified using standard microbiological techniques. The tip and side of the syringe used to inject the sterile normal saline were sampled for microbial contamination. The tip of the syringe was imprinted 10 times onto the surface of a blood agar plate. The syringe tip was pressed firmly onto the surface of

the agar for a period of 2 seconds. This process was repeated 10 times for each syringe. The sides of the syringe tip were then swabbed with a sterile cotton swab moistened with brain heart infusion broth (BHI). The swab was firmly placed onto the outer surface of the syringe nozzle and was rotated 5 times through 180°. The swab was subsequently inoculated onto a blood agar plate and processed as above.

The compression seal of the connector was sampled for microbial contamination by making impressions of the silicone seal and surrounding rim onto the surface of a blood agar plate. The silicone seal and surrounding rim of the connector was pressed firmly onto the surface of an agar plate for a period of 2 seconds. This process was repeated 10 times for each connector. The same process was repeated with the base of the connector. The compression seal and base of the connector whilst the impressions were being made were not contaminated. All plates were incubated and processed as described above.

4.3.1.1 *Results - Assessment 1*

The number of needleless connectors which allowed the passage of microorganisms following simulated clinical use and contamination of the compression seals with 1×10^4 organisms is shown in Table 4-1. Following disinfection with a 70% isopropanol swab, only 1 of 50 needleless connectors studied allowed microorganisms to pass through during injection of sterile normal saline *via* a syringe.

The numbers of microorganisms present on the syringe tips and the compression seals were also evaluated after use (Table 4-2) When the syringes were attached to disinfected devices, 19 of the syringe tips had no microorganisms present on their surface. Between 1 to 20 microorganisms were detected on the remaining syringe tips (mean 9.2 microorganisms). In comparison, 14 of the compression seals were sterile following disinfection. Of the remainder, 28 had <20 cfu and 8 had >20 cfu on their surface. When the 10 contaminated devices which were not disinfected were studied it was found that all had >20 cfu attached to their septa and syringe tip surfaces and all allowed >100 cfu to pass through with the sterile saline injection.

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Table 4-1   The number of Connecta Claves®, after contamination of compression seal with 1×10^4 *Staphylococcus epidermidis* (NCTC 9865), followed by disinfection with 70% isopropanol swabs or no disinfection, which subsequently allowed the passage of microorganisms during use. Sixty connectors were studied, 50 were disinfected and 10 acted as controls.

DISINFECTION	NUMBER OF CONNECTA CLAVES®			TOTAL STUDIED
	Number of Connecta Claves® which did not allow organisms to pass through	Number of Connecta Claves® which allowed organisms to pass through (1 – 100)	Number of Connecta Claves® which allowed passage of >100 organisms per ml	
YES	49	0	1	50
NO	0	5	5	10

Table 4-2 The number of microorganisms remaining on the syringe tips and compression seals following inoculation of 60 devices with 1×10^4 *Staphylococcus epidermidis* (NCTC 9865), followed by disinfection with 70% isopropanol swabs (50 connectors) or no disinfection (10 connectors).

DISINFECTION	NUMBER OF SYRINGE TIPS WITH:			
	No organisms detected	1 - 10 cfu detected	11 - 20 cfu detected	>20 cfu detected
YES	19	20	11	0
NO	0	0	0	10

	NUMBER OF COMPRESSION SEALS WITH:			
	No organisms detected	1 - 10 cfu detected	11 - 20 cfu detected	>20 cfu detected
YES	14	18	10	8
NO	0	0	0	10

4.3.2 Assessment 2 - Determination of compression seal microbial contamination in simulated clinical use

The number of microorganisms which may contaminate a needleless connector during routine clinical manipulation was determined. Ten healthcare workers manipulated one device each, as in the clinical situation. Each device was removed from its sterile packaging and held in the hand of the healthcare worker. The sterile male base cover of the connector remained in place. The connector was rotated 10 times, through 180° in the palm of the healthcare worker's hand. After handling, the connector was placed in a sterile universal container and was subsequently assessed for any microbial contamination, as above.

4.3.2.1 *Results - Assessment 2*

Of the 10 devices handled as in the clinical situation, 7 were found to be contaminated on their compression seals and associated rims with up to 16 cfu of skin microflora (range 2 -16, mean 5.2 cfu), predominantly CNS. The other three devices had no detectable microorganisms on their compression seal and associated rim.

4.3.3 Assessment 3 - Microbial contamination of needleless connectors when challenged with the same microbial load as detected in simulated clinical use

The compression seals of a further 60 sterile connectors were inoculated with 20 cfu of *S. epidermidis* as above (4.2.1). Fifty of the devices were cleaned with isopropanol swabs as described previously, 10 were not cleaned and acted as controls. A syringe was then attached to each device and 5 ml of normal saline was injected through. The number of microorganisms passing in the fluid, and present on the syringe tips were then determined, as above.

4.3.3.1 *Results - Assessment 3*

When 20 cfu of *S. epidermidis* were inoculated onto the compression seals of 50 devices, following disinfection with isopropanol, none of the microorganisms passed through with the injection of sterile normal saline. Of the syringes used to inject the normal saline through the device, 2 of the syringe tips had 2 cfu of *S. epidermidis* isolated. One compression seal had 3 cfu of *S. epidermidis* isolated from its surface. In comparison, when the 10 control devices which were not disinfected were examined, 2 allowed microorganisms to pass through.

4.3.4 Assessment 4 - Evaluation of different methods of needleless connector disinfection

A total of 160 needleless connectors were inoculated with 1×10^4 cfu *S. epidermidis*, as previously described, and placed at 37°C, in air, for 30 minutes to dry. Fifty devices were then disinfected with 70% isopropanol swabs as above. Fifty other devices were sprayed with chlorhexidine gluconate 2.5% v/v in IMS to produce a surface film of liquid, and subsequently allowed to dry, in air, at 20°C over 2 minutes. A further 50 devices were similarly disinfected with chlorhexidine, but this was followed by cleaning with isopropanol swabs, as before. Ten devices were not disinfected and acted as controls. The compression seal and surrounding rim of the connector were sampled 2 minutes after disinfection. A sterile swab moistened in sterile normal saline was firmly applied three times over the entire surface of each compression seal and rim. The swab was then inoculated onto a nutrient agar plate, which was incubated at 37°C in air and examined for microbial growth at 48 h.

4.3.4.1 *Results - Assessment 4*

The efficacy of 3 different disinfection schedules applied to the needleless connectors were evaluated. Of the three methods used, the combination of chlorhexidine gluconate 2.5% in IMS, followed by a 70% isopropanol swab, resulted in the greatest number of sterile devices (40 out of 50), although this was not statistically different ($p = >0.05$) from disinfection with isopropanol alone, which resulted in 32 out of 50 sterile devices. The

chlorhexidine in IMS proved least effective at disinfection, with only 16 out of 50 sterile devices. This was significantly different from the other two cleaning methods (p<0.05) using a Wilcoxon-Mann Witney Test. (Table 4-3).

Table 4-3   The number of Connecta Claves® (50) from which microorganisms were recovered following inoculation with 1 x 10⁴ *Staphylococcus epidermidis* (NCTC 9865) and disinfection with chlorhexidine 2.5% v/v in 70% industrial methylated spirit, 70% isopropanol swab, or a combination of both. All disinfectants were allowed to dry for at least 2 minutes prior to sampling.

METHOD OF DISINFECTION	NUMBER OF COMPRESSION SEALS AND ASSOCIATED RIMS WITH MICROORGANISMS			
	No growth	< 50 cfu	50 - 100 cfu	>100 cfu
Chlorhexidine 2.5% in IMS	16	28	5	1
70% isopropanol swab	32	16	1	1
Chlorhexidine 2.5% in IMS followed by 70% isopropanol swab	40	10	0	0

4.4   Discussion

Needleless connectors have been introduced into clinical practice in order to reduce risk of needle stick injuries, to prevent luers being inadvertently left open and to facilitate aseptic technique (Brown *et al.* 1997).   Their potential for contamination of peripheral cannulae and CVC, however has not been fully evaluated.   Conflicting reports to date suggest that such connectors may either be a potential source for microbial contamination particularly when aseptic techniques are questionable (Danzig *et al.* 1995), whereas other findings suggest that they are relatively safe to use (Adams *et al.* 1993).   In this part of the study the *in vitro* potential of a new type of needleless device was evaluated for microbial contamination.   The results demonstrated that when the needleless connectors were challenged with a relatively higher inoculum ($1x10^4$ cfu) than that found in the clinical situation after handling (16 cfu), and subsequently disinfected with 70% isopropanol swabs, the potential for microorganisms to pass *via* the device when injecting a fluid is less than 2%.   In comparison, when the compression seals were contaminated with 20 cfu, similar to that found in the clinical situation, no microorganisms were detected in the fluid injected through the device.   When using the Connecta Clave®, following contamination and disinfection, some of the tips from the syringes used to inject fluid through the device had microorganisms impacted onto their surface.   The device is specially designed to keep the external surface, including the compression seal, apart from the channel opened up for injection, thereby avoiding contamination.   This was confirmed by the finding that only 1 connector allowed microorganisms to pass when challenged with $1 x 10^4$ cfu, despite 36 out of 50 compression seals still having microorganisms on their surface post use, and none of the connectors allowed passage of microorganisms when 20 cfu were used.

The method of disinfection of needleless connectors needs to be given careful consideration in clinical practice.   Whereas it has been clearly demonstrated that disinfecting the device with 70% isopropanol swabs will reduce the risk of contamination, in critical areas where attention to asepsis needs to be given a greater priority, cleaning the device with chlorhexidine, followed by the use of a 70% isopropanol swab should be considered.

These findings suggested that in the clinical situation, with thorough and appropriate disinfection, the Connecta Clave® is unlikely to allow microorganisms to pass through during use. It was thought probable that the potential for contamination during use of these devices with either peripheral or central vascular catheters would be extremely low and that the Connecta Clave® may offer an advantage over other methods of intravenous connection. Luer ports for example, have a proven 23% contamination rate (Tebbs *et al.* 1996). Indeed it was considered that, if used appropriately, the Connecta Clave® would offer a decrease in the risk of microbial contamination of peripheral and central vascular catheters *via* the internal route.

In order to test the hypothesis that the Connecta Clave® should offer a decrease in the risk of microbial contamination of central vascular catheters *via* the internal route the device was evaluated in the clinical situation.

5. Determination of the potential of CVC microbial contamination when a needleless connector is used in clinical practice

5.1 Introduction

It was demonstrated in chapter 4 that *in vitro* the needleless connector, the Connecta Clave®, when challenged with microorganisms did not increase the potential risk for microbial contamination of CVC. The aim of this section of the study was to determine the potential for CVC microbial contamination when Connecta Claves® are used in clinical practice. Two hundred Connecta Claves® were to be studied in use.

5.2 Materials and Methods

Patients from the Haematology Unit at The Queen Elizabeth Hospital, Birmingham, who required a CVC as part of their medical management were recruited to the study following informed consent. All patients recruited had a Connecta Clave® aseptically attached to each lumen of their CVC. The CVC were not necessarily newly placed devices and were required for long-term intravenous therapy. The Connecta Claves® were left in place for up to 72 h or for a maximum of 72 activations. When each Connecta Clave® was removed it could be replaced with a further study connector. Each connector was subsequently examined for the presence of microorganisms.

5.2.1 Connecta Clave® attachment and use

An aseptic technique was employed by nursing staff during the process of attaching Connecta Claves® to CVC . Immediately prior to entry to the study the existing connector which was attached to the CVC hub was removed by the operator. The existing connector in all study patients was a needle-accessible device. To replace the existing connector the catheter side arm was clamped with non-toothed forceps and the

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connector removed from the catheter hub. The 3 cm distal portion of the catheter side arm was then placed in the centre of a folded, 70% isopropanol impregnated swab (Alcowipe®, Seton Healthcare, Oldham, UK), and the swab was then rotated around the catheter side arm, 5 times through 180°. The 70% isopropanol was allowed to dry for 2 minutes and a Connecta Clave® was then attached to the catheter hub. This process was repeated for each lumen of the catheter. Sterile gloves were worn throughout the procedures.

Each time the CVC was accessed, as described in section 4.2.1, an aseptic technique was used. The Connecta Claves® were cleaned using 70% isopropanol swabs (Steret®, Seton Healthcare, Oldham, UK). One isopropanol swab was used per connector. Each swab was firmly applied to the silicone surface and the associated rim of the Connecta Clave® and rotated through 180° five times. The devices were allowed to dry, in air, for 2 minutes prior to injecting or withdrawing fluid from the CVC. Although the findings in chapter 4 demonstrated that cleaning with chlorhexidine 2.5% in IMS followed by cleaning with a 70% isopropanol swab was the most effective method of disinfection, it was considered that in clinical practice this regimen would not be adhered to as it was time consuming having to wait for 2 cycles of disinfectant to air dry. The number of times each connector was accessed was documented. When blood was obtained from the CVC *via* the connector it was recorded.

5.2.2 Removal of Connecta Claves®

Each Connecta Claves® remained attached for up to 72 h, or for a maximum of 72 activations, whichever occurred first. All connectors were removed by the operator using a strict aseptic technique as described above, and were individually placed, silicone seal upright, in sterile universal containers. Care was taken not to touch the base of the connector during the removal process. All connectors were processed within 4 hours of removal from the CVC and were stored at 4°C if not processed immediately.

5.2.3 Determination of microbial contamination of the internal lumen of the CVC hub

When the Connecta Clave® was removed the internal surface of the CVC hub was sampled for microbial contamination. A cotton sterile swab (Sterlin, Copan, Italy), moistened with sterile normal saline was inserted into the catheter hub and rotated 180^0, 10 times. The swab was then inoculated onto a 7% blood agar plate which was incubated at 37°C in air and examined for microbial growth at 48 h.

5.2.4 Determination of microbial contamination of the Connecta Claves®

The compression seal of each connector, when removed, was cleaned with a 70% isopropanol swab as in clinical practice, (as described above), prior to microbiological sampling. A 1 ml syringe containing sterile BHI was then attached to the connector and 200 µl of the fluid flushed through the device. The 200 µl of BHI was collected in two 100 µl aliquots and each aliquot was inoculated onto a 7% blood agar plate. The plates were processed as described above.

The tip and side of the syringe used to inject the BHI were also sampled for microbial contamination, as described previously. The compression seal and base of the connector were sampled for microbial contamination by making impressions of the areas onto the surface of blood agar plates. This has been described in section 4.2.1.

5.2.5 Monitoring of infection

All patients were monitored daily for symptoms and signs of both local and systemic infection associated with the CVC. Symptoms and signs of local infection included; erythema, oedema, phlebitis, cellulitis, abscess formation and exudate from the CVC skin insertion site. The patients' core temperatures were also recorded. Symptoms and signs of systemic CVC related infection included the presence of 2 or more of the following; pyrexia following intermittent line flushing, no other obvious source of infection, pyrexia unresponsive to broad spectrum antibiotics, evidence of localised CVC infection or microbiological evidence of CVC associated sepsis. Any patients with evidence of

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systemic infection had blood taken for culture. If any CVC were removed due to suspected CRS the 5 cm catheter distal tip was examined for microbial contamination. The methods for determining microbial contamination of both the internal and external catheter lumen have been described previously.

5.3   Results

Over a 1 week period 5 patients were recruited into the study, 4 males and 1 female with a mean age of 53 years (range 39 - 65). All of the patients had double lumen CVC *in situ* of which 4 were Permacaths and 1 a Hickman catheter. The mean duration of catheterisation was 48 days (range 5 - 135). A total of 9 Connecta Claves® were studied in the above 5 patients. Two patients each received one connector, 2 patients received 2 connectors, and the remaining patient received 3 connectors.

5.3.1   Duration and use of Connecta Claves®
The mean length of time the connectors remained attached to CVC was 61.4 h (range 29 - 72 h). The connectors were accessed a mean of 10.6 times each (range 1-27 activations). None of the connectors had to be removed due to the maximum 72 activation limit being reached. All 5 patients received blood, blood products and chemotherapy through their CVC. Only 1 patient received intravenous antibiotic therapy *via* their catheter during the period of the study.

5.3.2   Microbial contamination of the internal lumen of the CVC hub
The microbiology of the catheter hub was determined in 3 patients. The hub swabs were all negative.

5.3.3   Microbial contamination of the Connecta Clave®

The number of Connecta Claves® which became contaminated during clinical use is shown in Table 5-1. Following disinfection 5 of the connectors (4 of the patients studied), allowed microorganisms to pass through during the injection of BHI. Of these, 4 connectors allowed the passage of microorganisms on both the first and second injection of fluid whilst the remaining connector only allowed microorganisms to pass through on the second injection of fluid.

Of the syringes used to inject the BHI through the connectors 3 had microorganisms isolated from the imprints of the syringe tips made onto blood agar plates. One connector had 1 imprint colonised with microorganisms, 1 had 6 imprints colonised and the remaining connector had 8 out of 10 of its imprints colonised with microorganisms. Of the swabs obtained from the sides of the syringe tips 2 were found to have microorganisms present on their surface. These results are shown in Table 5-2.

Each connector had 10 imprints of its silicone septum and surrounding rim made onto blood agar. Of the 9 connectors examined 4 had no microorganisms present on their surface. Of the remaining 5 connectors, 2 had 1 imprint colonised with microorganisms, 1 had 2 imprints colonised, 1 had 7 imprints colonised and from the remaining connector all the imprints had evidence of microbial growth. The total numbers and types of microorganisms isolated are shown in Table 5-2.

From the imprints made of the base of the connectors microorganisms were isolated from only 1 connector. From this connector 7 out of 10 of the imprints made had evidence of colonisation. The numbers and types of microorganisms isolated are also given in Table 5-2.

Table 5-1 The number of Connecta Claves®, after being used in clinical practice followed by disinfection with 70% isopropanol, which allowed the passage of microorganisms through the device.

Connecta Clave® No	Numbers and Species of Microorganisms Isolated	
	Flush Fluid	
	First 100 µl Fluid	**Second 100 µl Fluid**
1	19 cfu CNS	2 cfu CNS
2	340 cfu CNS	56 cfu CNS
3	No growth	No growth
4	No growth	1 cfu CNS
5	No growth	No growth
6	No growth	No growth
7	No growth	No growth
8	6 cfu CNS	24 cfu CNS
9	>1000 cfu CNS	>1000 cfu CNS

Table 5-2   The number of microorganisms remaining on the syringe tips and the side of the syringe tips after injection of brain heart infusion into Connecta Claves®.

Connecta Clave® No (5 patients)	Numbers and Types of Microorganisms Isolated			
	Syringe		Imprints	
	Tip (Imprint)	Side of Syringe	Silicone Seal and Surrounding Rim	Base
1	17 cfu CNS	No growth	No growth	No growth
2	No growth	No growth	13 cfu CNS	No growth
3	No growth	No growth	No growth	No growth
4	No growth	No growth	1 cfu CNS	No growth
5	No growth	No growth	1 cfu CNS	No growth
6	No growth	No growth	2 cfu CNS	No growth
7	No growth	No growth	No growth	No growth
8	1 cfu CNS	67 cfu CNS	No growth	No growth
9	48 cfu CNS	2 cfu CNS	72 cfu CNS 2 imprints gave confluent growth	35 cfu *S. epidermidis* 2 imprints gave confluent growth

5.3.4 Evidence of local and systemic catheter-related infection

Of the 5 patients included in the study none had evidence of localised CVC insertion site infection. During the 1 week study period none of the patients developed symptoms and signs of systemic CVC related infection. One patient however did have blood for culture taken 3 days post removal of the study connectors and this culture was positive. Subsequent blood cultures taken 7 and 10 days post connector removal were also positive. The patient from which the positive blood cultures were obtained had connectors numbers 8 and 9 attached to their CVC. Connector number 8 was attached to the blue lumen of the CVC whilst connector number 9 was attached to the red lumen. The patient, although initially apyrexial, went on to develop a low grade pyrexia ($< 38^{\circ}$C). Antimicrobial therapy was given for the treatment of the CRS. Although the patient initially responded to the antimicrobial therapy, the CVC was removed 5 days post finishing the course of treatment due to the development of a high grade pyrexia and rigors. The microbiological analysis of the 5 cm distal catheter tip was negative for both the internal and external lumen. This patient's microbiology results are shown in Table 5-3.

Table 5-3 Microbiological results from the patient who developed CRS and required CVC removal due to persistent clinical symptoms

Specimen	Date Obtained	Organism Isolated	Penicillin	Erythromycin	Vancomycin	Flucloxacillin
					Antibiotic Sensitivities	
Connecta Clave* No 8 (blue lumen)	19/7/96	*S. epidermidis*	S	S	S	S
Connecta Clave® No 9 (red lumen)	19/7/96	*S. epidermidis*	R	S	S	R
Blood Culture (lumen not stated)	22/7/96	*S. epidermidis*	R	S	S	S
Blood Culture (lumen not stated)	26/7/96	*S. epidermidis*	R	S	S	R
Blood Culture (lumen not stated)	29/7/96	*S. epidermidis*	R	S	S	R
Blood Culture (lumen not stated)	29/7/96	*S. epidermidis*	R	S	S	R
CVC Distal Tip - Internal lumen culture	2/8/96	No Growth				
External lumen culture	2/8/96	No Growth				

Key: S Sensitive
R Resistant

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5.4 Discussion

It was demonstrated in chapter 4 that *in vitro* the needleless connector, the Connecta Clave®, did not allow the passage of microorganisms through the device when it was challenged with 20 cfu. Twenty cfu of microorganisms represented the microbial load estimated to be present on the silicone surface of the device when used in clinical practice. The results from this section of the study however demonstrated that the devices, after use in clinical practice, did allow microorganisms to pass through despite thorough and appropriate disinfection. The compression seals of 5 connectors were found to have evidence of microbial contamination following cleaning, and of these 3 allowed microorganisms to be transferred from the silicone surface of the connector through the device when fluid was injected. These results suggest that the internal mechanism of the connector, which is specifically designed not to come in contact with the silicone seal and the connectors external surfaces, may have become contaminated during the injection process. Although 4 of the compression seals had no evidence of microbial contamination after cleaning, 2 had microorganisms recovered from the fluid injected through the device. The syringes used to inject fluid through these 2 connectors also had microorganisms recovered from their tips. The microorganisms isolated may have been present on the silicone surface of the connectors after cleaning with isopropanol swabs and were subsequently transferred to the syringe tips and the injection fluid during the injection process. The cleaning regimen for the connectors used in clinical practice was a 70% isopropanol swab. This cleaning method, as described in 4.2.4.1 was the most effective at removing microorganisms from the connector surface when a single disinfectant agent was chosen. Cleaning the silicone surface of the connector with chlorhexidine 2.5% in IMS followed by the use of an isopropanol swab may have resulted in less contamination of the devices, 4.2.4.1 however it was felt that in clinical practice this regimen would not be adhered to as it was time consuming due to having to wait for 2 cycles of disinfectant to air dry.

One patient who was included in the study developed a CRS 3 days post removal of the needleless device. Although 3 of the CNS isolated from the blood cultures had the same antibiotic sensitivity profiles as the microorganisms isolated from connector No 9, it is not

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possible to state with complete certainty whether the microorganisms originated from the connector, from within the CVC or were a result of haematogenous spread. The patient who developed CRS had their CVC in place for 69 days, therefore it is possible that the internal lumen of the CVC may have been colonised with microorganisms prior to the attachment of the Connecta Clave®. Colonisation of the CVC hubs was not evident when hub swabs were obtained however, colonisation may have occurred further along the internal lumen of the catheter. The catheter, which was removed due to the patient exhibiting persistent clinical symptoms and signs of CRS, when examined for microbial contamination was negative. Microbiological sampling of both the internal and external surfaces of the 5 cm catheter distal tip yielded no microorganisms but this may have been due to the patient receiving a course of intravenous antimicrobial therapy which was administered *via* the CVC.

The needleless connectors in this study demonstrated a microbial contamination rate of 55% which does not compare favourably with the reported 23% contamination rate of luer ports (Tebbs *et al.* 1996). Although the number of patients admitted to the study was small, the results suggest that if Connecta Claves® were used in clinical practice an increase in CRS may be observed. These results are consistent with the findings of Danzig *et al.* (1995) who reported an increase in septicaemia associated with needleless devices in patients who were receiving home therapy.

It was considered that due to the relatively high contamination rate of the needleless devices the study, being conducted with patients who were immunocompromised due to haematological disease, should be terminated. The source of microorganisms isolated from the needleless devices after being used in clinical practice was thought to have been from one of the following:

a) the silicone septum and subsequently injected through the device after in-effective cleaning regimens.

b) the injection of contaminated infusates

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c) microorganisms contaminating the CVC hub and/or the CVC internal surface and migrating to the internal surface of the needleless device

6. Determination of whether the CVC hub and/or the CVC internal surface are a potential source of Connecta Clave® microbial contamination

6.1 Introduction

To establish the source of microbial contamination of Connecta Claves® when they are used in clinical practice it was decided to assess whether of not the needleless devices became contaminated with microorganisms when they were attached to CVC in clinical practice but the devices not used. The purpose of not activating the devices would allow contamination from external sources to be excluded. Possible sources of external microbial contamination include: contamination of the silicone septum and microorganisms subsequently being injected through the device and the injection of contaminated infusates.

6.2 Materials and Methods

Twenty patients who underwent cardiothoracic surgery at the Queen Elizabeth Hospital, Birmingham who required a triple lumen CVC as part of their medical management were recruited to the study following informed consent. All CVC were inserted immediately prior to the planned surgical procedure and all patients required admission to intensive care post operatively. Patients were entered to the study at the time of discharge from the intensive care unit. All patients had 1 Connecta Clave® attached to one lumen of their CVC. Each connector was left in place for up to 24 h and during this time the connector was not accessed and therefore the lumen of the catheter on which the connector was placed was not subsequently used.

6.2.1 Connecta Clave® attachment and use

When a lumen of the CVC was no longer required for the infusion of either continuous or intermittent infusions a Connecta Clave® was attached. An aseptic technique was employed during the process of attaching the connectors. This technique has been described in section 5.2.1. Once the connector was in place the lumen of the catheter was clearly labelled with instructions for the device not be accessed and therefore the lumen of the CVC not to be used.

6.2.2 Removal of the Connecta Claves®

Each connector remained in place for up to 24 h and was then removed as described previously (section 5.2.2). All connectors were processed within 4 h of removal from the CVC and were stored at 4°C if not processed immediately.

6.2.3 Microbiological investigations

Microbial contamination of the: internal lumen of the CVC hub, the Connecta Clave®, the syringe tip used to inject fluid through the connector, the silicone surface and surrounding rim and the base of the connector were determined as described in sections 5.2.3 and 5.2.4.

6.2.3.1 *Determination of microbial contamination of the internal piercing element of the Connecta Clave®*

After the connectors had been flushed with BHI and imprints of the silicone seals and the bases made, the internal mechanism of the connector was also sampled. A straight sterile wire was passed through the split in the silicone seal and advanced to a depth of 1.5 cm. Once in position, the wire was rotated 5 times through 180° around the internal piercing mechanism. On removal the 1.5 cm of wire was rolled 5 times back and forth across the surface of a 7% blood agar plate. The blood agar plate was subsequently incubated at 37°C in air and examined for microbial growth at 48 h.

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6.2.4 Monitoring of infection

All patients were monitored daily for symptoms and signs of CVC related infection, as described previously.

6.3 Results

A total of 20 patients were recruited to the study, 17 males and 3 females with a mean age of 55 years (range 38 - 74). All patients had a triple lumen CVC *in situ* of which 18 were Deltacath® (Becton Dickinson, Meylan, France) and 2 were Braun (B-Braun, Melsungen, Germany). The mean duration of catheterisation prior to the attachment of the Connecta Claves® was 28.8 h (range 24 - 72 h).

6.3.1 Duration and use of Connecta Claves®

The mean duration of Connecta Clave® attachment was 20 h 15 min (range 7 h 50 min - 24 h). None of the connectors was accessed during the time they were attached to a CVC.

6.3.2 Microbial contamination of the internal lumen of the CVC hub

Microbiology of the catheter hub was determined in all patients studied. Nineteen (95%) of the CVC hubs studied were sterile whilst 2 cfu of CNS were isolated from the remaining catheter hub.

6.3.3 Microbial contamination of the Connecta Clave®

On removal 3 out of 20 (15%) connectors allowed the passage of microorganisms through the device following cleaning and flushing with BHI. One connector allowed CNS to pass through on both the first and second injection of fluid (5 cfu & 3 cfu respectively). One connector allowed microorganisms to pass through on the first

injection of fluid (1cfu CNS) and the remaining connector allowed 2 cfu of CNS to pass through on the second injection of fluid only.

Each syringe (100%) used to inject BHI through a device was analysed for microbial contamination. Microorganisms were not recovered from the swabs used to sample the side of the syringe tips or from the imprints made of the tip of the syringes on to blood agar plates.

Each connector had 10 imprints of its silicone septum and surrounding rim made onto blood agar. Of the 20 connectors examined 1 had evidence of microbial contamination. One cfu of CNS was isolated from the silicone surface of this connector.

From the imprints made of the base of the connectors, microorganisms were isolated from 2 connectors. One connector had 2 cfu of CNS present and the remaining connector had 1 cfu of CNS isolated.

6.3.4 Microbial contamination of the internal piercing element of the Connecta Clave®

The internal piercing elements of the connectors were sampled in all 20 patients, all were negative.

6.3.5 Evidence of local and systemic catheter-related infection

Of the 20 patients studied none had evidence of either local or systemic CVC-related infection. Blood cultures were therefore not obtained from any patient.

The positive microbiology results from all the assessments are shown in Table 6-1

Table 6-1   The number and species of microorganisms isolated from Connecta Claves® after being attached to CVC in clinical practice but not accessed. The silicone seals of the connectors were disinfected with a 70% isopropanol swab prior to assessment, as in clinical practice.

Patient Number	Lumen Swab	Flush Fluid		Imprints	
		First 100μl	Second 100μl	Silicone seal & surrounding rim	Base
7	NG	5 cfu	3 cfu	1 cfu	2 cfu
8	NG	1 cfu	NG	NG	NG
10	NG	NG	2 cfu	NG	NG
11	2 cfu	NG	NG	NG	NG
13	NG	NG	NG	NG	1 cfu

NG = No microbial growth

6.4 Discussion

It was demonstrated in chapter 5 that once used in clinical practice 55% of Connecta Claves® allowed the passage of microorganisms through the device following cleaning with a 70% isopropanol swab. When the connectors were attached to CVC and not used the passage of microorganisms through the device was reduced to 15%. Although the transfer of microorganisms was reduced to a quarter, the results did not reflect the findings of the *in vitro* assessments which demonstrated that the needleless devices did not allow the passage of microorganisms following disinfection.

The source of the microorganisms leading to the contamination of the needleless devices when attached to CVC and not used remains unclear. It was considered that the microorganisms may have originated from the catheter hub and migrated into the internal mechanism of the Connecta Claves®. However this seems unlikely as microorganisms were isolated from only 1 catheter hub, and the connector removed from this catheter was sterile. The base of 1 connector had a single colony of CNS isolated from it however this cannot be attributed to microorganisms migrating from the CVC hub to the connector as the hub of the catheter lumen was sterile. The connector which had microorganisms isolated from the flush fluid and from the imprints made of the silicone surface and base had a negative hub swab, this suggests that the microorganisms gained access to the connector via the silicone seal and not from the internal lumen of the CVC.

The numbers of microorganisms isolated from the connectors in this section of the study were small and the patients studied did not exhibit any clinical symptoms and signs of CRS, however the connectors were only left in place for up to 24 h and not used. If the connectors were left in place for up to the manufacturer's recommended 72 h the numbers of microorganisms present may have increased therefore increasing the risk of CRS.

It has been clearly demonstrated that within the laboratory the needleless connector the Connector Clave® compares favourably with the already widely used luer ports. The results are however less favourable when the Connector Clave® is used in clinical practice. The assessments conducted on connectors that had been used in clinical practice demonstrate that the needleless device the Connecta Clave® may increase the risk of microbial contamination of central venous catheters via the internal route. Indeed, these results support the findings of Chodoff et al. (1995) who raised concerns regarding patient safety when such devices were used.

This limited clinical evaluation of the needleless device, the Connecta Clave®, has highlighted the need for additional studies to be conducted on such devices before they are used routinely in the clinical area. The following areas of study should be considered:

Firstly, is the cleaning of needleless devices of an effective standard when carried out in clinical practice? It has been demonstrated in this study that microbial contamination of needleless devices, and of the fluid flushed through them, when carried out in a controlled environment, is minimal. The increase in microbial contamination when the devices are used in clinical practice may therefore be due to ineffective cleaning regimens. Controlled 'cleaning trials' are needed on connectors in clinical use to evaluate further this hypothesis.

Secondly, it is necessary to establish the source of microorganisms contaminating needleless devices. To determine the exact source of microbial contamination samples for microbial analysis should be taken from all parts of the connector as well as from the CVC hub and the patient. Any microorganisms isolated should then be typed by PFGE. By using this sensitive and accurate typing method it should be possible to establish whether microorganisms contaminating the needleless devices originate from within the CVC and migrated to the internal mechanism of the connectors or whether the microorganisms originate from the silicone surface of the connector and are injected through the device during drug/fluid administration.

Thirdly, not all the components of the needleless device particularly the internal surface of the piercing mechanism were sampled for microbial contamination. These components may play an important role in the continued contamination of these devices and add additional risks to patients. Mechanisms for microbiology sampling the internal components of needleless devices need to be designed.

7. The cost of infections related to CVC designed for long term use

7.1 Introduction

Synthetic intravascular catheters were introduced for hospital use in the 1940's (Meyers, 1945) and have since formed an essential part of patient management. Intravascular devices are used widely throughout the world, however, they are associated with many complications including infection. Catheter-related sepsis is a significant clinical problem having a recognised associated morbidity and mortality (Elliott, 1988). The reported incidence of infective complications associated with CVC is reported to be between 3.8 and 12% (Maki *et al.* 1973). Goldman and Maki (1973) similarly reported that 7% of patients having total parenteral nutrition developed bacteraemia. Press *et al.* (1984) demonstrated a 14.4% infection rate in patients with Hickman catheters.

The cost of CVC associated infections has previously not been determined directly and estimates have involved many assumptions. The Kings Fund Centre (1992) reported that, for patients receiving total nutrition, the cost of a catheter-related infection varied from £1,650 to £5,000. These estimates were based on case scenarios. The lower figure of £1,650 was for a patient with an increased hospital stay of seven days in a general ward. Bacteriology requests, antibiotic therapy, intravenous fluids and disposables were included in the costs. In comparison, a higher figure of £5,000 was calculated for a patient with an increased hospital stay of 10 days who required care on a high dependency unit. This estimate included the cost of CVC replacement. These costs involved applying estimated average costs for various services and procedures, including antibiotic therapy and bacteriology tests. Besides the Kings Fund report no other studies have directly determined the cost of CVC-related sepsis.

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There were three objectives in this study:

a) To directly calculate all additional costs incurred by patients whilst hospitalised due solely to an infection associated with a CVC designed for long term use.

b) To calculate the annual potential overall cost of long term CVC-related infections to the NHS.

c) To estimate the annual potential overall cost of short term CVC-related infections to the NHS.

7.2   Methods

7.2.1   Patient selection

Over a 12 month period, patients who presented to either the haematology or oncology wards at the Queen Elizabeth Hospital, Birmingham, UK with a presumptive diagnosis of a CVC-related systemic infection were prospectively entered into this part of the study. Evidence of catheter-related infection was based on clinical symptoms and signs and/or positive blood cultures. If a different diagnosis was subsequently made these patients were withdrawn from the study. Patients who acquired a CVC-related infection whilst in hospital were not included in the study. The costs subsequently calculated were obtained from information on patients who were admitted and specifically treated for a community acquired systemic CVC-related infection and discharged from hospital following treatment only for the infection.

7.2.2   Measurement of costs

The parameters assessed for calculating the cost of CVC-related infection included laboratory costs (microbiology, haematology and biochemistry), antibiotic therapy and associated drug level monitoring, catheter removal and any replacement or

peripheral cannula insertion. The non pay costs included consumables used to carry out procedures and the hotel costs of the patient's hospital stay. Healthcare personnel's time in delivering care specifically related to the CVC infection was also recorded. Cost were determined based on the following sources: antibiotic costs from the British National Formulary (1995); laboratory costs identified by the hospital laboratory manager and consumable costs from the National Health Supplies Catalogue (1995). Hotel costs were provided by the Clinical Directorate Finance Manager. All items utilised were recorded and the central cost calculated. The hotel costs encompassed the following; energy, catering, domestics, sterile services, laundry, portering, maintenance, food production, medical engineering, medical illustration, transport, capital and medical physics. The hotel costs were calculated on an 'overnight stay' basis per patient, which represented a 24h period. Nursing, medical and administration personnel's time was also included in the 'overnight stay' calculation. The perspective of this analysis was that of the NHS, it therefore excluded indirect and intangible costs.

7.2.3 Data collection

The treatment and any investigations carried out on the patient were recorded and a cost allocated. Procedures that either a doctor or nurse carried out on the patient were timed. These included venesection, antibiotic administration and temperature monitoring. All associated consumables were listed for each procedure and the cost determined. All costs were computed using Microsoft Excel 5.0 (Microsoft Corporation, USA). Length of hospital stay was also recorded.

7.3   Results

Twenty patients were recruited into the study, 15 male and 5 female with a mean age of 49 years (range 25 -77). All patients had a CVC *in situ* at the time of hospital admission. Fourteen patients (70%) had a Hickman catheter, 5 (25%) had a Permacath catheter and the remaining patient a Portacath catheter (5%). The mean number of days the catheters were *in situ* up to admission into the study was 236 days (range 15 - 1464). The reasons for admission to hospital were pyrexia of unknown origin only (95%) or positive surveillance blood cultures (5%). After clinical assessment on admission all the patients were diagnosed as having a CVC-related infection based on having two or more of the following symptoms and signs; pyrexia with no obvious source of infection, pyrexia following intermittent line flushing, pyrexia unresponsive to broad spectrum antibiotics, or evidence of local infection around the catheter insertion site.

At the time of admission to hospital, blood for culture was obtained from the study patients. A single bottle culture was obtained from 17 patients of which 12 (67%) were positive. Two patients had 2 blood cultures and one patient had a set of 3 blood cultures taken, all of these were positive. The blood for culture was obtained *via* a CVC in all patients, 1 patient had blood taken via a peripheral vein and a CVC. A total of 13 single bottle cultures were also subsequently obtained from the hospitalised patients of which 5 (25%) were positive.

All patients received antibiotic therapy for their CVC-related infection. The mean length of antibiotic treatment was 7.2 days (range 2 - 13 days) with an average associated cost of £607.76. For initial treatment 6 (30%) patients received monotherapy (vancomycin or teicoplanin), 12 (60%) patients combination therapy (piperacillin and gentamicin, vancomycin and ceftazidime or ceftazidime and flucloxacillin), and 2 (10%) patients triple therapy (ceftazidime, vancomycin and piperacillin).

The mean length of hospital stay due to a CVC-related infection was 7 days (range 3 -13) with an associated cost of £1094.12. This was calculated from the 'overnight stay' cost provided by the Finance Director. This included the time taken by nursing and medical staff caring for the patients. The treatment given specifically related to a CVC infection including venesection, antibiotic administration and temperature monitoring, amounted to a total of 87 hours nursing time and 28 hours medical time. Five (25%) patients in the study had their CVC removed due to persistent infection. The cost of catheter removal and the associated microbiological analysis of the distal tips was incorporated into the mean costs. One catheter was removed due to the catheter splitting. The remaining 14 (70%) catheters were left *in situ* and the CVC-related infection treated successfully. Laboratory investigations included: blood cultures, antibiotic drug level monitoring, catheter tip analysis, CVC exit site swabs and white cell counts in the blood. These cost on average £93.74 per patient. The total mean cost of a CVC-related infection in this study was £1781.81 (Table 7-1 and Figure 7-1). A breakdown of the components used to calculate the cost of these infections is shown in Table 7-2.

Table 7-1 **Mean total costs of treating 20 patients with infections related to long term central venous catheters.**

ITEM	MEAN COST	95% CONFIDENCE INTERVALS
Laboratory investigations	£93.74	£75.99 - £111.49
Antibiotic prescription and delivery costs	£607.76	£428.08 - £787.43
Hotel costs	£1094.12	£905.79 - £1282.46
Total cost per infective episode	£1781.81	£1445.90 - £2117.73

Table 7-2   An example of the costs of individual components used to calculate the financial burden of an infection related to CVC designed for long term use.

ITEM	COST (£)
Negative CVC skin insertion site swab	8.00
Positive blood culture	15.00
Drug level monitoring - six samples	90.00
Positive CVC tip analysis	10.00
Serum white blood cell count - three samples	9.60
Antimicrobial therapy	206.05
Sterile consumables used for blood sampling, drug administration and catheter removal	198.79
Hotel costs - nine days	1348.92
TOTAL	**1886.36**

Figure 7-1   Total costs of infections related to CVC designed for long term use
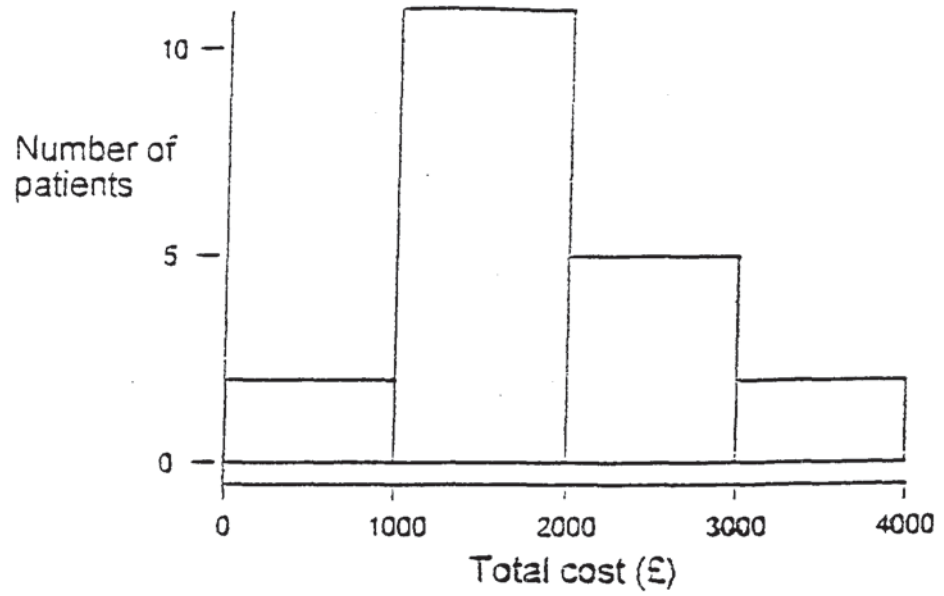
7.4 Discussion

In this study the mean cost of a CVC-related infection was calculated to be £1781.81 per episode. This cost compares with the Kings Fund (1992) 'best case scenario' estimate of £1650 for a patient receiving total parenteral nutrition who developed a catheter-related infection. None of the patients studied in this investigation required treatment on a high dependency unit. A direct comparison to the Kings Fund 'worst case scenario' which estimated that a CVC-related infection requiring 10 days high dependency care could cost £5000 was not therefore made. It is, however, apparent from current studies that, of all the patients with long term indwelling CVC, less than 0.1% will require high dependency care for such infections (Elliott and Bowen, personnel communication). The majority of the financial burden of CVC-related infections therefore relates to patients who are treated in the ward situation rather than high dependency units.

Approximately 10,000 CVC designed for long term use are used annually in the UK. If a 14.4% infection rate, as reported by Press *et al.*(1984) is applied to this figure, 1440 infections associated with these catheters occur per annum. Based on the calculations in this study this represents an annual cost of £2,565,906 to the NHS. The cost of infections related to catheters designed for long term use, including Hickman and Permacath catheters, however cannot be directly applied to those used for short term. The difference in the clinical management of patients with infections associated with either short or long term catheters are likely to result in significant variance in cost. Devices used for long term therapy are usually more intensively treated with antimicrobials in order to salvage the catheter. In comparison, patients with short term catheters usually have the device removed earlier as part of their management and will not require antimicrobial therapy. This in turn may result in earlier discharge from hospital. Stricter sterile precautions are also usually taken when administering therapy via a catheter designed for long term use as compared to short term catheters, this includes the use of additional sterile consumables. These differences in clinical approach to the two types of CVC must therefore result in an increase in cost associated with long term catheter-related infection. The cost of infections associated with short term use CVC are however likely to be considerable as approximately 190,000 are used annually in the UK with an associated systemic infection

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rate of 4%. If the costs of infections related to catheters designed for long term use, as calculated in this study, were applied to short term use catheters, the cost would be approximately £13,000,000 per annum. However, due to the differences in clinical management of the short term catheters, it is likely that the actual cost is between £5,000,000 to £7,000,000 per annum. Further analysis is required to determine more accurately this financial burden. Interestingly, if the hospital directorates' 'blanket' daily charge were applied to the mean hospital stay for CVC related infection, as calculated in this study, the mean cost of each CVC infective episode would amount to £1684.47. This is comparable to the mean cost determined in this study.

To reduce the monetary cost of CVC-related infections and to improve the quality of care given to patients with these devices many strategies have been applied. These include: improved education programmes; the introduction of specialist intravenous nursing teams (Puntis *et al.* 1990); and early diagnostic testing (Henry *et al.* 1983) with associated directed antimicrobial treatment, some of which may be carried out at home. Home antimicrobial therapy should be considered as a means of reducing hospital stay. This study demonstrated that hospital inpatient stay accounted for a large proportion of the total cost incurred for a patient with a central venous catheter-related infection. Home intravenous antimicrobial therapy has been demonstrated to be both safe and effective in the treatment of serious bacterial infections. Grayson *et al.* (1995) reported that home treatment was not only well tolerated with no significant complications, but it also reduced bed use and allowed additional hospital throughput. Home therapy may not however, reduce hospital costs. The increase in throughput of patients, which home therapy may bring, means the vacated hospital bed could potentially be occupied by a patient who requires more costly treatment and prolonged hospitalisation, thereby increasing overall costs.

Antimicrobial therapy in this study accounted for 34% of the mean total cost of treatment associated with CVC-related infection. Intravenous antimicrobial therapy accounts generally for 30 - 40% of the total Pharmacy drug acquisition budget (Guglielmo and Brooks, 1989). To reduce antimicrobial costs several approaches have been considered including: therapeutic equivalence; the use of cheaper preparations which have a similar spectra of activity, efficacy and adverse event profiles, and the selection of long acting

agents which allow reduced frequency of administration. Other approaches to reduce costs has been to change from intravenous to oral therapy and the use of a restricted formulary (Guglielmo and Brook, 1989., Maleck *et al.* 1992., Briceland *et al.* 1988., Pizzo *et al.*1986., Tanner & Nazarian 1984., Quintiliani *et al.* 1986). At the Queen Elizabeth Hospital, Birmingham where this study was conducted, choice of antimicrobial therapy is guided by the hospital's Consultant Microbiologists with a strict antibiotic policy in place (Burdon *et al.* 1995).

Methods to facilitate the speed of diagnosis of CVC-related infections are required so that appropriate antimicrobial treatment can be commenced without delay. At present the diagnosis of CVC-related infection is difficult to make as the symptoms and signs can be non specific and definitive microbiological results are only available after the device is removed. Emmerson *et* al. (1996) reported that the degree of certainty in diagnosing infection related to central venous catheters was 55.5%. Rapid accurate diagnosis by improved methods may not only improve patient outcome but cost savings could be made both in reducing the duration of antimicrobial therapy and length of hospital inpatient stay.

Prevention of CVC associated infection also needs to be considered as a cost saving strategy. Measures which should be considered include: improved aseptic techniques; adequate skin preparation; the use of topical antimicrobial agents; the development of antimicrobial CVC (Tebbs and Elliott, 1993) and even by the application of electric current to devices to reduce catheter colonisation (Crocker *et al.* 1992).

This study demonstrated that CVC associated infection has significant cost implications for the National Health Service. The mean cost per patient of an infection associated with a long term catheter was shown to be £1781.81. In the UK this amounts to £2,565,906 per annum, with the likelihood of short term catheter-related infections costing between 5 to 7 million pounds per annum. Inpatient stay accounted for a large proportion of the total cost incurred for these patients with an infection related to a CVC. Improved methods of prevention of catheter-related sepsis, earlier diagnosis and use of home therapy could reduce costs and allow a reduction of the current significant financial burden.

8. A prospective clinical study to investigate the efficacy of a CVC impregnated with benzalkonium chloride

8.1 Introduction

Many approaches have been taken to reduce the incidence of CRS. These have ranged from improved education of healthcare workers in the insertion and care of CVC and the modification of catheter polymers. Modification of polymers has included the development of hydrophilic catheter surfaces and more recently the incorporation of antibiotics and antiseptics. The use of catheters impregnated with antibiotics is, at present, clinically limited due to the concern of encouraging resistant microorganisms. In comparison, the use of antiseptic impregnated CVC is likely to be more widely accepted as resistance to antiseptics is unlikely. A catheter impregnated with chlorhexidine and silver sulphadiazine is currently available and has been demonstrated to reduce the incidence of CRS in intensive care patients (Ramsey *et al.* 1994., Raymond and Steinberg, 1994., Trazzera *et al.* 1995., Lovell *et al.* 1995., Maki *et al.* 1997). The objectives of this section of the study were to determine, *in vivo*, the safety of CVC impregnated with BZC and to assess the efficacy of the catheters. Central venous catheters impregnated with BZC were compared to a standard uncoated polyurethane CVC.

8.2 Materials and methods

8.2.1 Patient selection

Two hundred patients who were admitted to the Queen Elizabeth Hospital, Birmingham and required a CVC as part of their clinical management were recruited to the study following informed consent. Patients were invited to participate in the study if it was considered they may require a CVC for at least 3 days. Patients were recruited to the study over a 12 month period. Patient exclusion criteria included: being under 18 years of age, pregnant or lactating women, a known history of allergy or sensitivity to BZC or if patients had previously been enrolled in the study.

8.2.2 Study design

Once patient consent had been obtained a study catheter was randomly assigned to that individual. Patients were assigned to either the BZC catheter group or the control group. The randomisation system consisted of sequentially sealed envelopes each of which contained information stating the specified study catheter the patient should receive. The study was open, comparative, controlled, and randomised.

8.2.3 Catheters

Both catheters were non-cuffed, triple lumen, 7 French and 20 cm in length. The control catheters were made from polyurethane (Deltacath™, Becton Dickinson, Meylan, France). The test catheters were also polyurethane and in addition had a hydrophilic and antimicrobial coating on the internal and external surfaces (BZC) (Hydrocath Assure™, Ohmeda, Swindon, UK). The catheters were distinguishable from one another due to the colour of the catheter body. The control catheter was yellow whereas the test catheter was white.

8.2.4 CVC insertion

An aseptic technique was used by the medical staff for the insertion of the CVC. The catheter skin insertion site and surrounding area was sprayed with chlorhexidine 2.5% in IMS (DuPuy Healthcare, Leeds, UK), until a surface layer of moisture was present, this was allowed to air dry for 2 minutes. Sterile drapes were then placed around the proposed CVC insertion site and associated non-clean areas. All the catheters were inserted by Seldinger technique (Soni, 1996) and the number of attempts at cannulation was documented. The catheters were inserted to varying depths, which were recorded, depending on the size of the patient and the position of the CVC. The grade of physician inserting the catheter, along with the hospital location where the procedure took place, was also documented. Once in place the catheter skin insertion site was again disinfected with chlorhexidine gluconate in methylated spirit, as described above, and allowed to air dry for 2 minutes prior to the attachment of a dressing. The dressings used to cover the

CVC insertion sites were non-occlusive and transparent and each covered an area of 10 cm by 13 cm (Tegaderm™, 3M, Borken, Germany).

8.2.5 Determination of patient risk factors associated with the development of infection

At each catheter insertion the following was documented whether or not the patient was receiving: ventilatory support, tracheostomy, steroids, chemotherapy, inotropes, haemodialysis, total parenteral nutrition and surgery. A history of solid organ transplantation was also recorded. Any underlying risk factors were also recorded including: diabetes mellitus, hypoalbumaemia, renal insufficiency, malignancy, neutropenia, major trauma, burns, HIV and a urinary catheter. The patients anaesthesiology classification of physical status was determined according to the American Society of Anaesthesiology scoring system (ASA). The classifications of the scoring system are shown in Table 8-1 The number and type of additional intravascular devices *in situ* at the time the study catheter was inserted were also recorded.

Table 8-1   American Society of Anaesthesiology classification of physical status

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Class 1

The patient has no organic, physiological, biochemical or psychiatric disturbance. The pathological process for which the operation is to be performed is localised and does not entail a systemic disturbance.

Class 2

Mild to moderate systemic disturbance of distress caused by either the condition to be treated surgically or by other pathophysiological processes.

Class 3

Severe systemic disturbance or distress from whatever cause, even though it may not be possible to define the degree of disability with finality.

Class 4

Severe systemic disorders that are already life, not always correctable by operation.

Class 5

The moribund patient who has little chance of survival but is submitted to operation in desperation.

Adapted from Brown, 1995

8.2.6 Comparison of serum sodium and serum potassium levels when blood is taken *via* the study CVC and from an alternative site

Immediately following catheter insertion a 4 ml sample of blood was taken *via* the distal lumen of the CVC. A further 4 ml sample was then taken from either an arterial catheter, if the patient had one in place, or from a separate peripheral stab. The blood samples were placed in separate vacutainer[®] bottles and clearly labelled. The samples were processed within 1 h of being obtained from the patients. All serum sodium (Na^+) and serum potassium (K^+) levels were determined using a direct reading ion selective electrode analyser (CIBA, Corning, UK).

8.2.7 CVC insertion site care

The CVC skin insertion site was observed daily for signs and symptoms of localised CVC-related infection (section 2.2.7). CVC insertion site dressings were changed according to ward protocols. If there was evidence of any of the following the CVC dressings were changed sooner: infection, elevation or detachment of the dressing causing the CVC insertion site to be exposed, or a collection of blood or moisture below the dressing. At each dressing change an aseptic technique was followed. After removal of the dressing the CVC insertion site was cleaned with sterile gauze moistened with sterile normal saline. The site was than sprayed with chlorhexidine gluconate 2.5% in IMS until a surface layer of moisture was observed, this was allowed to air dry for 2 minutes and a sterile dressing applied, as described above. Each dressing change was documented.

8.2.8 Determination of catheter use

The administration of antimicrobial therapy and/or blood sampling *via* the CVC was recorded The frequency of administration set changes was also documented. The patency of the catheter lumen was also recorded daily.

8.2.9 Determination of catheter tolerability

Each patient, throughout the time the study CVC was in place, was monitored daily for symptoms and signs of catheter-related adverse events. Catheter-related adverse events were defined as any undesirable clinical occurrence that may be attributable to the CVC.

8.2.10 Monitoring of infection

Patients were monitored daily for symptoms and signs of local and systemic CRS. Clinical evidence of local CVC-related infection included; erythema, oedema, purulent and/or clear exudate from the CVC skin insertion site. The patient was asked, when possible, if they had any sensation of pain or irritation at the catheter insertion site. Symptoms and signs of systemic CVC-related infection included pyrexia unresponsive to broad spectrum antibiotics, no other obvious source of infection and/or microbiological evidence of CRS. If CRS was suspected blood for culture was obtained *via* the CVC and also from a peripheral venepuncture.

8.2.11 Removal of CVC

The decision to remove the study CVC was made independently by the medical team caring for the patient. The reasons for catheter removal were documented and may have included: accidental, treatment ended, local inflammation, venous thrombosis, breakage, patient death, CRS, occlusion, pyrexia of unknown origin, local infection or other. On removal of the study CVC it was documented if re-catheterisation was carried out.

All CVC were removed aseptically. Immediately after the dressing covering the CVC insertion site had been removed a skin swab was obtained from around the CVC insertion site. This method has been described in section 2.2.8. The CVC skin insertion site was then cleaned with sterile gauze soaked in sterile normal saline and sprayed with chlorhexidine gluconate 2.5% in IMS, as described previously, and allowed to air dry for 2 minutes. The CVC was explanted by applying gentle pressure to the proximal end of the device. Once removed, the 6 cm distal tip of the CVC was dissected with a sterile blade from the catheter body and the tip placed in a sterile universal container. The same process was repeated for the 3 cm subcutaneous portion of the device. The subcutaneous

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portion of the device was defined as the 3 cm length of catheter immediately below the skin insertion site. Once the catheter body had been dissected the three-way taps attached to the catheter were removed. Care was taken not to contaminate the catheter hubs. A swab of the internal lumen of each catheter hub was obtained, as described in section 2.2.6. All microbiological samples were stored at 4°C until processed.

8.2.12 Determination of the number of microorganisms at the CVC skin insertion site at the time of CVC removal

The swabs taken from the $2cm^2$ area surrounding the CVC skin insertion site were processed as described in section 2.2.3.

8.2.13 Determination of the number of microorganisms present within the CVC hub

To establish if any microorganisms were present on the internal surface of the CVC hubs a swab of each port was taken. A sterile cotton swab moistened in Triton X-100 (0.1%) was placed in the hub entry port and rotated 180°, 10 times. The swab was then placed in 2ml of STM and the number of microorganisms contaminating the swab was determined. Each swab was vortex mixed for 60 s and then a 100 µl aliquot of the STM was inoculated onto the surface of a 7% blood agar plate. The blood agar plates were incubated for a period of 48 h at 37°C in 5% CO_2. The remaining STM was placed in 10 ml of brain heart infusion broth and incubated overnight as described previously. Any broths which had visible evidence of microbial growth were subcultured onto 7% blood agar plates and incubated for a 24 h as described above. Any microorganisms present were enumerated and identified using standard microbiological techniques.

8.2.14 Determination of the number of microorganisms present on the CVC external surface on removal

The numbers and types of microorganisms colonising the outer surface of the distal and subcutaneous portions of the catheters were determined by the roll plate method (Maki et al. 1977), (section 2.2.8).

8.2.15 Determination of the number of microorganisms present on the CVC internal surface on removal

Microbial contamination of the internal surface of the CVC was determined by flushing the distal lumen with 1 ml of STM containing lecithin and tween, as described in section 2.2.8. This process was repeated for the middle and proximal lumen. All the microbiological plates were incubated for 24 h at 37°C in 5% CO_2 and processed as described previously.

8.2.16 Determination of zones of inhibition

An overnight culture of *S. epidermidis* NCTC 11047 in nutrient broth was standardised to a concentration of 1×10^6 cfu/ml, as described in section 4.2.1. A 100 µl of the suspension (1×10^6 cfu/ml) was then inoculated on to a nutrient agar plate and spread evenly over the surface of the agar using a sterile cotton swab. The suspension was left to air dry at 20°C for 20 minutes before the distal portion of the explanted catheter was placed onto the surface of the agar plate. The plates were subsequently incubated at 37°C in air for 24 h. The zone of inhibition produced by the catheters was measured by vernier callipers. The zone measurements were read from the widest area of inhibition perpendicular to the catheter segment's long axis. This was repeated for the 3 cm subcutaneous portion of the catheter.

8.2.17 Statistical Analysis

Statistical analysis was conducted using the chi-square test, unless otherwise stated. All analysis were computed using Statview®5 (SAS Institute Inc. Cary USA)

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8.3 Results

8.3.1 Patient characteristics

A total of 200 patients were recruited into the study of which 166 were evaluable. Of those patients considered non-evaluable 22 were randomised to receive control catheters and 12 antiseptic catheters. Patients were non-evaluable due to; the catheters not being available for culture in 32 patients, 1 catheter not being placed, and a technical problem with a further device. Of the 166 evaluable patients 88 (53%) received antiseptic catheters and 78 (47%) received control catheters. The patients in each group were similar in both age and sex. In the antiseptic catheter group there were 57 (65%) males and 31 (35%) females with a mean age of 58.6 years (range 20 - 85 years). Of those patients studied in the control catheter group 44 (56%) were male and 34 (44%) were female with a mean age of 60.9 years (range 25 - 86 years). All patients immediately post CVC-insertion underwent major surgery. The type of surgery carried out on each patient is shown in Table 8-2.

The patients studied were similar for risk factors predisposing to nosocomial infection including the experience of the operator inserting the catheter, the number of attempts at cannulation and the ASA score. The number of attempts at cannulation ranged from 1 - 6 attempts in the antiseptic catheter group and 1 - 7 in the control patient group. The median number of attempts at cannulation was 1 in both groups. The blood vessels into which study CVC were placed are shown in Table 8-3. The ASA score ranged from 1 - 4 in both groups with a median score of 2 in the antiseptic catheter group and median score of 3 in the control CVC group.

Table 8-2   Type of surgery carried out on the 166 evaluable patients following CVC insertion

CATHETER	TYPE OF SURGERY (Number of patients)				
	Hepato-biliary	Cardiac	Oesophageal	Gastrointestinal	Gynaecological
Antiseptic (*n* = 88)	48	29	5	5	1
Control (*n* = 78)	38	23	11	3	3

Table 8-3   Patient's blood vessel cannulated with study CVC

Catheter	Vessel Cannulated (Number of Patients)			
	Left Internal Jugular Vein	Left Subclavian Vein	Right Internal Jugular Vein	Right Subclavian Vein
Antiseptic (*n* = 88)	10	1	76	1
Control (*n* = 78)	10	I	64	3

8.3.2 Monitoring of serum sodium and serum potassium levels

Serum sodium and serum potassium were measured in 62 (70.4%) patients in the antiseptic catheter group and serum sodium in 46 (58.9%) and serum potassium in 45 (57.6%) of the patients in the control group. Each patient had blood taken through their CVC and a further sample was taken from a separate venepuncture site, each patient acted as there own control. In the antiseptic catheter group the mean difference between the serum sodium levels obtained *via* the antiseptic CVC and those obtained from an alternative site was -0.177 mmols/l (range - 7.00 to +7.00 mmols/l). The mean difference in the serum potassium levels was 0.042 mmols/l (range - 0.300 to +0.900 mmols/l). The mean difference in the serum sodium levels obtained from the control group as compared to samples taken from alternative sites was - 0.478 mmols/l (range -10.000 to +6.000 mmols/l). The mean difference in the serum potassium levels was -0.018 mmols/l (range -1.000 to +1.000).

8.3.3 Duration of catheterisation

The mean duration of catheterisation with a study CVC was 3.69 days (range 1 - 11 days) in the antiseptic catheter group in comparison to 4.33 days (range 1 - 12 days) in the control group. The difference in duration of catheterisation was not significant
$(p = 0.1701$, Mann-Whitney U test). Each patient entered into the study had other means of IV access besides the study CVC. The number of other IV catheters *in situ* ranged from 1 -6 devices (mean 3) in the antiseptic catheter group and 1 - 7 (mean 3) in the control group.

8.3.4 Catheter use and catheter care

All catheters were used for the administration of fluids, drugs and for monitoring of central venous pressure. In the antiseptic catheter group 87 (98.8 %) patients received antibiotic therapy and in the control catheter group 77 (98.7 %) patients received antibiotic therapy. There was no difference in the number of CVC-insertion site dressing changes that were carried out in each group.

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8.3.5 Catheter tolerance

There was no significant difference between the two groups in the incidence of erythema, oedema and purulent exudate at the CVC skin insertion sites (Table 8-4). Pain was reported by 1 patient in the control group. None of the study patients developed symptoms and signs of catheter-related adverse events.

8.3.6 Catheter complications

There was a significant difference in the numbers of catheters that migrated out of position in the control catheter group and of those that kinked at the skin insertion site in the antiseptic catheter group. These results are demonstrated in Table 8-5. The number of catheter lumen that became blocked was similar in both groups.

8.3.7 Evidence of CVC-associated infection

8.3.7.1 *Local CVC-associated infection*

One patient in the antiseptic catheter group developed evidence of localised CVC-associated infection, however this was not statistically significant from the control catheter group ($p = >0.1$).

8.3.7.2 *Systemic CVC-associated infection*

None of the patients studied had evidence of systemic catheter-related sepsis. Twenty one patients (12.6%) developed a pyrexia >38°C however, these were unrelated to the study CVC. Blood for culture was obtained in 28 (16.8%) patients, 12 (43%) from the antiseptic catheter group, and the remaining 16 (57%) from the control catheter group. Of all the blood cultures obtained only 1, taken from a patient in the control group, became positive. The microorganism isolated from this culture was CNS, the site from where the blood for culture had been drawn was not stated.

Two patients in the antiseptic catheter group had their CVC changed due to the length of time the device had been in place. Prior to catheter removal blood for culture was

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obtained, all cultures were negative. In the control catheter group 2 patients had their device removed due to a pyrexia of unknown origin. Blood for culture was obtained from both patients prior to catheter removal and each culture was negative.

8.3.8 Catheter removal

The decision to remove the study CVC was taken by the medical team caring for the patient. One hundred and sixty one (97%) of the CVC were removed by the same the operator. The reasons for catheter removal are highlighted in Table 8-6.

Table 8-4   Number of patients exhibiting signs of catheter intolerance at the CVC skin insertion site

Variable	Antiseptic Catheter Skin Insertion Site ($n = 88$)	Control Catheter Skin Insertion Site ($n = 78$)
Erythema	21	25
Oedema	1	4
Purulent Exudate	1	0
Pain	0	1

Table 8-5   Number of study catheters that were associated with kinking or migrating out of position

CATHETER	COMPLICATION	
	Number of Catheters which Kinked	Number of Catheters which Migrated
ANTISEPTIC	24*	1**
CONTROL	4*	9**

*p = 0.0001
**p = 0.0049

Table 8-6   Reason for removal of study CVC

Reason for Catheter Removal	Number of Catheters Removed	
	Antiseptic Catheter	Control Catheter
Treatment Ended	78	74
Occlusion/Kinking	4	1
Local Infection	1	0
Death	2	0
Pyrexia of Unknown Origin	0	2
Catheter changed due to length of time *in situ*	2	0
Catheter in wrong position	0	1
Haematoma	1	0
Total	**88**	**78**

* 1 patient had CVC replaced.

8.3.9 Microbiology results

All catheters were processed within 2 to 42 h of removal (mean 13.4 h). There was no difference between the 2 groups in the time taken to culture the devices. The antiseptic catheters were processed in a mean of 13.7 h (range 2.2 to 25.5 h) in comparison to a mean of 13.1 h (range 3 to 42 h) for the control group.

8.3.9.1 *Microbial colonisation of the CVC-skin insertion site*

Eighty six patients (97.7%) from the antiseptic catheter group and 77 patients (98.7%) from the control catheter group had their CVC-skin insertion site sampled immediately prior to device removal. There was no significant difference between the number of colonised insertion sites in both groups. In the antiseptic catheter group 55 (62.5%) of patients had colonised insertion sites in comparison to 49 (62.8%) patients in the control group. Table 8-7 below shows the distribution of the microorganisms isolated.

There was a correlation between the number of microorganisms isolated from the skin insertion site and the external surface of the CVC distal tip in the antiseptic catheter group (r = 0.3792 (p = 0.0003) Spearman rank correlation). This correlation was not demonstrated in the control catheter group. There was a correlation in both catheter groups between the number of microorganisms isolated from the skin insertion site and the number recovered from the external surface of the subcutaneous segments of the CVC (antiseptic catheters r = 0.4146 (p = <0.0001) control catheter r = 0.2784 (p = 0.025) Spearman rank correlation).

The predominant microorganism isolated from the skin insertion sites was CNS. Coagulase negative staphylococcus was isolated from 47 (85.4%) of the antiseptic catheter group skin insertion sites and from 41 (83.6%) of the control catheter group. The remaining insertion sites were colonised with *S. aureus*, gram-negative aerobic bacilli, enterococci or *Candida* species.

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Table 8-7   Microbial colonisation at the CVC skin insertion site immediately prior to device removal.

NUMBER OF CFU ISOLATED	TYPE OF CATHETER	
	ANTISEPTIC (Number of Patients)	CONTROL (Number of Patients)
0	33	29
1 - 20	16	13
>20 - 100	6	4
>100 - 1000	13	14
>1000	20	18

8.3.9.2 *Microbial colonisation of the CVC hubs*

The number of catheter hubs contaminated with microorganisms was similar in both groups. In the antiseptic catheter group 85 (96.5%) patients had all 3 hubs sampled and of these 36 (42.3%) had 1 or more colonised hubs. In the control catheter group 76 (97.4%) patients had all 3 hubs sampled and of these 32 (42.1%) had 1 or more colonised hubs. The predominate microorganism isolated from the catheter hubs in both groups was CNS.

8.3.10 Catheter microbial colonisation

8.3.10.1 *External surface - Distal tip*

Microbial colonisation of the external surface of the 6 cm distal tip was determined in 88 (100%) patients in the antiseptic catheter group and in 78 (100%) patients in the control catheter group. Microorganisms were isolated from 19 (21.5%) of the antiseptic catheters and from 32 (41%) of the control catheters ($p = 0.0055$). Microbial colonisation of ≥ 15 cfu was present on 10 (11.3%) antiseptic catheter distal tips and 18 (23%) of the control catheter distal tips ($p = 0.0356$). There was no difference between the two groups when catheters colonised with ≥ 100 cfu were compared and similarly when catheters colonised with ≥ 1000 cfu were compared. There was a correlation in both groups between the

number of days the CVC remained *in* situ and distal tip external surface microbial colonisation (antiseptic catheter $r = 0.330$ ($p = 0.0015$) control catheter $r = 0.2842$ ($p = 0.0117$) Spearman rank correlation). The predominate microorganism isolated in both of the catheter groups was CNS.

8.3.10.2 *External surface - Subcutaneous section*

Microbial colonisation of the external surface of the 3cm subcutaneous section of the CVC was determined in 85 (96.5%) patients in the antiseptic catheter group and in 69 (88.4%) patients in the control catheter group. Microorganisms were isolated from 14 (18.6%) of the antiseptic catheters and from 24 (34.7%) of the control catheters ($p = 0.0075$). There was no significant difference between the 2 groups when the following levels of contamination were determined; ≥ 15 cfu and ≥ 100 cfu. None of the catheters in either group were colonised with ≥ 1000 cfu. In the antiseptic CVC group there was a correlation between the number of days the device remained *in situ* and microbial contamination of the external surface of the subcutaneous section of the device ($r = 0.3638$ ($p = 0.0006$) Spearman rank correlation). This correlation was not demonstrated in the control catheter group. The predominate microorganism isolated in both catheter groups was CNS.

8.3.10.3 *Internal surface - Distal tip*

Eighty seven (98.8%) of the antiseptic catheter group had the 6 cm distal tip internal surface of each catheter lumen examined, this was in comparison to 74 (94.8%) of the control group. The was no significant difference between the 2 catheter groups when microbial colonisation rates in; the distal, middle or proximal lumen were compared. Seventeen (19.5%) of the antiseptic group had between 1 and 3 lumen colonised in comparison to 21 (28.3%) in the control group ($p = 0.1292$). Sixteen (18.3%) of the antiseptic catheter group had a total of ≥ 20 cfu isolated from the catheter internal surface in comparison to 20 (27%) in the control group ($p = 0.1312$). In the antiseptic catheter group there was a correlation between distal tip internal surface microbial colonisation and the number of days the device remained *in situ* ($r = 0.2945$ ($p = 0.0053$) Spearman rank

correlation). This correlation was not seen in the control catheter group. The predominate microorganism isolated in both catheter groups was CNS.

8.3.10.4 *Internal surface - Subcutaneous section*

The internal surface of the 3 cm subcutaneous section of the CVC was examined in 84 (95.4%) of the antiseptic catheter group and in 70 (89.7%) of the control group. Fourteen (16.6%) in the antiseptic catheter group had between 1 and 3 lumen colonised in comparison to 22 (31.4%) in the control group $(p = 0.0248)$. There was a significant difference in microbial colonisation of the internal surface of the subcutaneous distal lumen of each catheter. Five (5.9%) of the antiseptic catheter group had ≥ 20 cfu isolated from the distal lumen internal surface in comparison to 13 (18.5%) in the control group $(p = 0.0148)$. There was no significance difference observed when comparisons were made between isolation of ≥ 100 cfu and ≥ 1000 cfu in the subcutaneous distal internal lumen. The internal surface of the middle and proximal lumen were examined and comparative microbial colonisation rates were not significant. In the control CVC group there was a correlation between microbial colonisation of the subcutaneous internal lumen of the catheter and the number of days the device remained in place $(r = 0.2784$ $(p = 0.0205)$ Spearman rank correlation). This correlation was not demonstrated in the antiseptic catheter group. The predominant microorganism isolated in both catheter groups was CNS.

A summary of external and internal microbial colonisation of the distal tips is shown in Table 8-8. Microbial colonisation of the external and internal subcutaneous catheter sections are shown in Table 8-9.

Table 8-8   Microbial colonisation of the 6 cm distal tip of both external and internal catheter surfaces.

Surface of Catheter Examined	DISTAL TIP (6 CM)				
	Antiseptic Catheter		Control Catheter		p
	Number Colonised	%	Number Colonised	%	
External (> 0 cfu)	19	21.5	32	41	0.0055
External ($\geq$ 15 cfu)	10	11.3	18	23	0.0356
Internal (>0 cfu)	17	19.5	21	28.3	0.1292
Internal ($\geq$ 20 cfu)	16	18.3	21	28.3	0.1292

Table 8-9   Microbial colonisation of the 3 cm subcutaneous section of both external and internal catheter surfaces.

Surface of Catheter Examined	SUBCUTANEOUS SECTION (3 CM)				
	Antiseptic Catheter		Control Catheter		p
	Number Colonised	%	Number Colonised	%	
External (> 0 cfu)	14	18.6	24	34.7	0.0075
External ($\geq$ 15 cfu)	9	10.5	12	17.3	0.1617
Internal (>0 cfu)	14	16.6	22	31.4	0.0248
Internal ($\geq$ 20 cfu)	14	16.6	21	30	0.0381

8.3.11 Zones of inhibition

8.3.11.1 *Distal tip (6 cm)*

The distal tip zone of inhibition was determined in 88 (100%) of the antiseptic catheter group and in 78 (100%) of the control catheter group. Zones were present in 24 (27.2%) of the antiseptic catheter group and in 4 (5.1%) of the control group $(p = < 0.0002)$. The mean maximum zone size surrounding the distal section of the antiseptic catheters was 11.2 mm (range 4 - 23 mm) this was in comparison to a mean of 15.25 mm (range 13 - 17 mm) for the control catheters.

8.3.11.2 *Subcutaneous section (3cm)*

The antimicrobial activity of the subcutaneous section of the catheters was determined on device removal. Subcutaneous zone of inhibition was determined in 85 (96.5%)of the antiseptic catheter group and 69 (88.4%) of the control catheter group. Zones of inhibition were present around 35 (41.1%) of the antiseptic catheter group and 4 (5.7%) of the control catheter group $(p = <0.0001)$ The mean maximum zone size surrounding the subcutaneous portion of the antiseptic catheters was 9.34mm (range 5 - 28 mm) in comparison to a mean of 8 mm (range 9 - 11 mm) in the control group.

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8.4 Discussion

Central venous catheter polymers have been bonded with antibiotics and antiseptics in order to decrease the risk of catheter colonisation and subsequent CRS. The bonding of antibiotics to CVC has not been embraced by clinical practice due to concerns regarding the emergence of antibiotic resistance. The bonding of antiseptics to polymers has however been met with greater clinical acceptance. It has previously been demonstrated *in vitro* that BZC prevented bacterial colonisation of catheter surfaces (Tebbs and Elliott, 1993, 1994), however this current study reports for the first time the efficacy of using such a device in clinical practice. The results have demonstrated that by using a catheter impregnated with BZC the incidence of catheter microbial colonisation is reduced. The reduction in microbial colonisation was evident on the external distal and subcutaneous surfaces of the CVC as well as on the internal surface of the subcutaneous section of the catheter. The BZC catheter was tolerated by all study patients and there were no reports of catheter related adverse events.

The mechanism by which BZC interferes with microbial colonisation is unclear. It has been suggested that BZC may have an effect on microorganisms closely aligned to the catheter surface and inhibit microbial attachment. Alternatively, BZC may have a bactericidal effect once catheter colonisation has occurred (Tebbs and Elliott, 1993). The results from this study suggest that microorganisms are prevented from attaching to the catheter surface due to the action of BZC leaching from the CVC. However, there also appears to be some antimicrobial activity on the CVC surface. This was evident as some patients who received BZC catheters had microorganisms isolated from the CVC surface, however the numbers were reduced in comparison to those who received a control catheter. The reduction in microorganisms was particularly evident at the distal tips of the CVC.

Antimicrobial catheters may also reduce the numbers of microorganisms at the CVC skin insertion site. However a reduction in microbial colonisation at the insertion sites of those patients who received BZC catheters not found. Why a reduction was not observed is not clear. It may be due to several factors including; the type of dressing used to cover the

insertion site, the amount of moisture that came into contact with CVC at the insertion site or due to the presence of protein which may reduce the activity of BZC (Hugo and Russell, 1992). Despite there being no difference in the numbers of microorganisms isolated from the skin insertion sites of both patient groups, the BZC catheter was effective in reducing catheter colonisation on the external surface of the CVC. Extraluminal contamination from the CVC puncture site is one of the main sources of microbial contamination leading to CRS (Wistbacka and Nuutinen, 1985). This study has therefore demonstrated that by using a BZC impregnated CVC the risk of CRS from this mode of microbial spread can be significantly reduced albeit with a similar microbial load at the skin insertion site.

Microbial contamination of the catheter external surface can occur at the time of device removal. In this study to minimise the possibility of this mode of contamination the patient's skin insertion site surrounding the CVC was cleaned with sterile normal saline and sprayed with chlorhexidine gluconate 2.5% in IMS immediately prior to catheter removal. This reduced the numbers of microorganisms present on the skin surface prior to device removal. The mean time taken from removal to processing the catheters was similar in both groups. It was considered important to standardise the storage of the microbiology samples as well as the time interval between CVC removal and sampling. Details of the time taken between CVC removal and microbiological processing and/or storage conditions of the specimens have not been stated in similar studies examining the efficacy of antimicrobial CVC (Maki et al. 1997., Logghe et al. 1997., Heard et al. 1998). If catheters are not processed immediately the action of the antiseptic catheters may continue despite having being explanted. Similarly, if catheters are not stored at 4°C prior to processing microorganisms present on the control CVC may continue to multiply whilst microorganisms on the test catheter may be inhibited by the antiseptic present on the CVC surface.

Zones of inhibition from the BZC antiseptic catheters were recorded in 27% of the distal tips and in 41% of the subcutaneous tips post device removal. Zones of inhibition were present in both sections of the CVC for up to ten days. This is consistent with the work conducted by Tebbs and Elliott (1993) who reported that *in vitro* BZC catheters retained

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their activity for at least seven days. The zone of inhibition test conducted in this study concentrated on measuring BZC leaching from the catheter at the time of removal. Despite some BZC catheters on removal not exhibiting a zone of inhibition the catheter surface may still have had a bactericidal effect. The explanted antimicrobial CVC would have to be directly challenged with microorganisms onto the catheter surface in order to test this theory further.

The patients from both groups in this current study had similar CVC hub colonisation rates. Despite both groups being challenged with the comparable microbial loads *via* the internal route there was a significant reduction in microbial colonisation in the internal lumen of the subcutaneous section of the BZC catheters. There was also a marked reduction in internal distal tip microbial colonisation however this did not reach significance. The reason there was a significant difference in internal microbial colonisation at the subcutaneous section of the catheter and not at the distal tip is unclear. This difference may be due to: the difficulty in sampling the internal lumen of the distal tip or an uneven distribution of BZC on the internal surface of the catheters. Flushing the internal lumen of the 3 cm subcutaneous portion of the CVC is uncomplicated due to each lumen terminating at the same point. However, sampling the internal lumen of the 6 cm distal tip is technically more difficult due to 2 of the 3 lumen terminating at points located on the side of the catheter body. As sampling fluid is flushed through the proximal and middle lumen of the distal tip there is the possibility of microbial contamination occurring as the fluid may come into contact with the catheter's external surface. Any microorganisms which may not have been removed during external surface sampling may contaminate the flush fluid used to sample the internal lumen of the CVC. To combat this problem sampling of the internal lumen of the CVC could be carried out by using an endoluminal brush. Sampling the internal surface of the dissected catheter segments using this method may minimise the risk of external surface contamination.

To demonstrate that BZC is incorporated throughout the internal lumen of the CVC zone of inhibition testing of the internal CVC surface would be required. The catheters could be dissected longitudinally through each lumen and zones of inhibition determined as described previously (section 8.2.16). However, practically this would be difficult to perform due to the small size of the lumen and due to the cylindrical shape of the

catheter. Additional testing methods need to be developed in order to assess the distribution of BZC within the internal lumen. The internal route of microbial colonisation has been demonstrated as being as important as the external route as the source of microorganisms causing CRS (Logghe *et al.* 1997). Microorganisms that originate from the CVC catheter hub migrate down the internal lumen of the CVC and colonise the distal tip. Logghe *et al.* (1997), who studied the chlorhexidine silver sulfadiazine catheter in patients with leukaemia suggested that these antiseptic catheters did not prevent CRS from occurring as they allowed intraluminal bacterial migration. The chlorhexidine silver sulfadiazine catheter does not offer internal antimicrobial protection. In the current study the incidence of microbial colonisation *via* the internal lumen was reduced and therefore may prevent the development of subsequent CRS.

Of the 166 patients recruited to the study none developed symptoms or signs of CRS. This does not compare with the incidence of CRS reported in similar studies conducted using antiseptic catheters (Maki *et al.* 1997., Logghe *et al.* 1997., Heard *et al.* 1998). The absence of CRS in the current study may have been due to: the relatively short period of time the study CVC remained in place, the vessel in which the catheter was placed, the type of patients studied and/or the effectiveness of the skin antiseptic used prior to catheter insertion and at all subsequent CVC dressing changes. The mean duration of CVC cannulation in the present study was 3.9 days. It is recognised that the risk of CRS increases with prolonged catheterisation (Richet *et al.* 1990., Ullman et al. 1990). The antimicrobial activity of the BZC catheter has been demonstrated in this study to be up to ten days and may even extend this period, therefore greater benefits of the BZC antiseptic CVC may be observed when the catheters remain in place for longer periods of time. Maki *et al.* (1997), in their study investigating the effectiveness of a CVC impregnated with chlorhexidine gluconate and silver sulphadiazine demonstrated a reduction in both catheter colonisation and catheter-related bloodstream infection, the catheters remained in place for a mean of six days. However studies assessing the efficacy of the same catheter in patients who required longer term catheterisation reported there was not a reduction in the incidence of catheter related bacteraemia (Logghe *et al.* 1997., Heard *et al.* 1998). The lack of reduction in catheter related bacteraemia was associated with internal lumen colonisation. The BZC catheter has antimicrobial protection on its internal lumen and it is

is envisaged that prolonged catheterisation would not increase the risk of CRS from this source.

The BZC catheter, in this study, was prone to kinking at the CVC skin insertion site. The kinking of the catheters was probably due to the relatively thin walls of the catheter body. It was noted through the duration of the study that if kinking of the antiseptic CVC occurred the device did not recover its original shape when manipulated. Of the non-evaluable CVC one of the antiseptic catheters was not inserted due to technical difficulties. The technical difficulty was due to the operator not being able to feed the CVC over the guidewire. An explanation for this could be that the lumen of the catheter may have become narrowed due to the impregnation of BZC. The control catheters in the current study had a higher incidence of migrating out of position in comparison to the antiseptic catheter group. The secondary fixation device used to hold the control CVC in place were not as effective as that used on the BZC catheter. The catheters in the control group could move through the fixation device and migrate out of the vessel. This potentially could have adverse implications as drugs and fluids may be infused into the patients tissues as opposed to into the vein.

Benzalkonium chloride has been associated with elevated serum sodium and serum potassium levels when blood samples were taken *via* heparin-bonded umbilical catheters (Gaylord *et al.* 1991). In the current study there was no significant difference between the serum sodium and potassium levels obtained *via* the BZC catheter in comparisons to those taken as a control from a separate venepuncture site. Indeed, there was a wider range of results between the serum sodium and serum potassium levels when blood was obtained *via* the control CVC and a separate venepuncture than from BZC catheters.

This study has demonstrated that CVC incorporated with BZC on both the internal and external surface can reduce the incidence of catheter microbial colonisation when used in patients requiring short term catheterisation. This reduction in colonisation may potentially reduce the incidence of CRS for those patients who require a CVC for prolonged periods of time. The BZC catheter was tolerated by patients who received a device and there was no evidence of toxic effects from the BZC that leached from the catheters whilst *in situ*. The BZC catheter can be used safely within clinical practice and

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offers a means by which the incidence of catheter colonisation can be reduced. Further studies need to be conducted on patients who require a CVC for longer than 4 days to determine if the BZC catheter is effective in reducing the incidence of CRS.

9. General Discussion

The skin is recognised as being a major source of microorganisms contributing to catheter colonisation and CRS. Microorganisms migrate extraluminally from the patient's skin down the external surface of the catheter to the distal tip (Elliott, 1988). This study has demonstrated that microbial contamination from the skin can also occur at the time of catheter insertion. Microorganisms are impacted onto the distal tip of the CVC during the insertion procedure, this is despite the use of aseptic techniques and thorough skin disinfection. It is evident that the use of current skin antisepsis is not able to eliminate all the patient's resident skin microflora. Microorganisms remain both on the skin surface and within the deeper skin layers (section 2.4). This study has also demonstrated that when CVC are introduced *via* a protective sheath avoiding contact with the skin, the incidence of catheter colonisation is reduced but it is not completely eliminated (chapter 3). The use of modified catheter cuffs, for example those impregnated with silver compounds act as a tissue-interface barrier (Jansen, 1997). These cuffs provide some protection from microorganisms migrating from the patient's skin surface along the length of the device however, they would not prevent the impaction of microorganisms on to the catheter distal tip at the time of insertion. The use of an antimicrobial catheter impregnated with BZC on both external and internal catheter surfaces may however reduce the likelihood of this source of sepsis. This study has demonstrated that there was a significant reduction in catheter colonisation when a BZC impregnated catheter was used in comparison to a non-impregnated device (chapter 8)

Various strategies have been applied in order to reduce the incidence of CVC colonisation and CRS. These strategies have mainly concentrated on the reduction of microbial colonisation of the external catheter surface and have included methods to reduce microbial migration from the skin surface to the CVC distal tip. These preventative strategies have included: modified cuffs, antimicrobial dressings, topical antimicrobials and the inclusion of antiseptics onto the external surface of the CVC (Jansen, 1997., Hoffman *et al*. 1992., Maki *et al*. 1994., Kaye and Smith, 1988., Maki *et al*. 1997). It is now well recognised however that the internal route of microbial migration is as important in the development of CRS as the external route particularly in those patients who require

catheterisation for > 8 days (Sheretz, 1997). Microorganisms originating either from the patient's own skin microflora or from that of the healthcare worker may contaminate the CVC hub and subsequently migrate, or are flushed, down the catheter lumen.

Modified catheter hubs and connectors, for example the betadine connection shield, have been designed in order to reduce internal catheter colonisation. These modified hubs have been successfully trialled however there use is limited in clinical practice. (Segura et al. 1990., Halpin et al. 1991).

Needleless intravascular connectors have recently been introduced in order to reduce the risk of bloodborne infections to healthcare workers. There have been suggestions that such devices may even reduce the incidence of catheter colonisation (Adams et al, 1993). It has been demonstrated in this study that *in vitro* the needleless device, the Connecta Clave®, when challenged with microorganisms did not allow the passage of microbes through the device when fluid was injected. It was therefore concluded that the needleless device should not increase the risk of catheter colonisation or CRS (chapter 4). Once the needleless connector was used in clinical practice it was demonstrated that microbial contamination of the device was higher than the routinely used luer connector (section 8.3.10.3). This increase may have been due to: a lack of compliance by healthcare workers to adhere to the strict cleaning regimens needed in order to prevent microbial colonisation. or due to microbial contamination of the connectors' internal mechanisms. It was not possible in this study to determine the exact origin of the microorganisms associated with needleless connector contamination. It was concluded that by using such a device there was an increased risk of internal lumen colonisation and CRS.

Internal lumen catheter colonisation is an area of CVC care that has continued to be a problem despite efforts being made to overcome it. This study has demonstrated that by impregnating a CVC with the antiseptic BZC on the internal surface the incidence of intraluminal colonisation is reduced. By decreasing microbial colonisation from this source the incidence of CRS may also subsequently be reduced. Due to the mean length of time the catheters in this study remained in place (BZC catheters 4.3 days and control catheters 3.6 days) it was impossible to determine whether the CVC impregnated with

BZC would reduce the incidence of CRS. Antimicrobial activity was demonstrated at both the distal tip and subcutaneous portion of the antiseptic catheters when challenged with microorganisms after the device had been in place for up to 10 days. It is therefore anticipated that BZC catheters left in place for prolonged periods of time would be associated with a reduced incidence of CRS. Further studies are needed to confirm this.

The cost to the NHS of infections associated with long term CVC was demonstrated to be in excess of £2.5 million per annum. The figure was estimated to be between £5 and £7 million for those infections associated with short term CVC (chapter 7). In this study the use of a antiseptic impregnated CVC reduced microbial colonisation by almost 50%. If the antiseptic catheter reduced the incidence of CRS by up to 50% considerable cost savings may be made. The cost of purchasing a device impregnated with an antiseptic would be more expensive than a non-coated catheter however, the benefits such a device could offer would off set the increased purchasing cost.

To reduce the monetary cost of infections associated with CVC, antimicrobial devices impregnated with an antiseptic on both the internal and external surface should be introduced alongside improved education programmes. The use of an antimicrobial catheter in this study did reduce the incidence of catheter colonisation. These novel antiseptic catheters should not however be introduced as a compromise for poor aseptic technique at the time of catheter insertion and at all subsequent catheter care.

Further work

The impaction of microorganisms onto the distal tip of BZC catheters.

Microorganisms were impacted onto the distal tips of 17% of CVC when they were inserted through the skin (chapter 3). The catheters used in this study were un-coated polyurethane CVC. It would be of interest to determine whether, if by using an antimicrobial CVC, the incidence of microbial contamination at the time of catheter insertion would be reduced. The combination of a Hydromer® and BZC coating may prevent microorganisms from becoming impacted on to the catheter distal tip at the time of insertion.

Improved skin antiseptic delivery systems

It has been reported that chlorhexidine gluconate is more efficacious than povidone iodine and 70% isopropanol in the prevention of CRS (Maki et al, 1991). However it was demonstrated in section 2.3.1 that the skin antiseptic chlorhexidine gluconate 2.5% in IMS was not effective in removing all microorganisms from the skin surface prior to catheter insertion. Microorganisms were also recovered from dermal layers of the skin. This study has highlighted the need for further work to be conducted within the area of skin antisepsis. Future work should concentrate not only on the development of new and improved skin antiseptics but also on mechanisms by which skin antiseptics can be delivered to the deeper skin layers.

The controlled use of the needleless connector the Connecta Clave®

The Connecta Clave®, when evaluated *in vitro*, did not allow the passage of microorganisms through the device despite some microbes being isolated from the silicone surface post injection of fluid. These results suggested that the device when used in practice would not be of additional risk to patients (chapter 4). However, in practice, the contamination rate of the needleless was higher than the routinely used connector. Further studies are needed to fully establish the origin of the microorganisms contaminating the needleless devices when they are used in clinical practice. Controlled trials need to be conducted in which the method of device antisepsis should be closely monitored. All microorganisms isolated should be typed and PFGE conducted as

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appropriate. By carrying out such specific typing methods it should be possible to identify the source microbial contamination. By identifying the source of microbial contamination it can be determined whether clinical practice in the care of such devices needs to be changed, or indeed if the design of the connectors needs to be reconsidered.

The use of BZC impregnated CVC in patients who require catheterisation for >10 days

The BZC impregnated catheter did reduce the incidence of catheter colonisation (chapter 8) however, due to the relatively short cannulation period it was impossible to determine whether a reduction in CRS would be achieved. Similar studies conducted on immunocompromised patients who received a catheter impregnated on the external surface with chlorhexidine gluconate and silver sulphadiazine reported that the incidence of CRS was not reduced in those patients who required catheterisation for prolonged periods of time (Logghe et al, 1997., Heard et al, 1998). It was suggested that a reduction in CRS was not demonstrated due to the catheter only having antiseptic present on one catheter surface. It would be of interest to ascertain whether the BZC catheter, which has antiseptic impregnated onto both surfaces, reduced the incidence of CRS when prolonged catheterisation is required.

Zone of inhibition testing of the internal surface of the BZC impregnated catheter

In the present study zone of inhibition testing was conducted on the external surface of the subcutaneous section and distal tip of the BZC catheter (section 8.2.16). It would be of interest to also determine the level antimicrobial activity within the internal lumen of the CVC at the time of device removal. Zone of inhibition testing of the internal surface would clarify how long internal surface antimicrobial activity was present. It should also be possible, by this method, to determine if BZC is evenly distributed along the internal surface of the catheter.

Retained bactericidal effect of BZC on explanted catheters

Zone of inhibition testing on explanted CVC determined whether BZC leached from the catheters at the time of removal (section 8.1.16). To determine whether bactericidal activity were present on the explanted antiseptic CVC, the surface of the catheter segments could be directly challenged with microorganisms. By this direct antimicrobial challenge a correlation between the length of time the catheter remained *in situ* and retained bactericidal activity could be determined.

Possible future CVC developments

Incorporation of antimicrobials into catheter hubs and connectors

It has been clearly demonstrated in this study that CVC hubs and connectors are a major source of microorganisms which cause catheter colonisation and may result in subsequent CRS (chapters 5 & 6). The impregnation of catheter polymers with antimicrobials has demonstrated that a reduction in microbial colonisation can be achieved. It would be advantageous if the technology of antimicrobial impregnation could be applied to catheter hubs and connectors. The incorporation of antimicrobials into these ports may reduce microbial colonisation from these sources and in turn reduce the incidence of CRS.

Incorporation of antimicrobials to CVC designed for long-term use

The use of antimicrobial CVC is, at present, limited to those patients who require short-term catheterisation. The leaching of antimicrobials from catheter polymers is limited to periods of approximately 10 days. This study has demonstrated that infections associated with CVC designed for long-term use, for example Hickman catheters, incur a substantial cost to the health service (chapter 7). A method to reduce infections associated with long-term CVC and subsequently reduce costs may be to develop polymers through which the release of antimicrobials could be sustained for prolonged time periods.

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APPENDIX 1