COMPARISON OF 14-DAY CATHETER-RELATED INFECTION RATES BETWEEN STANDARD AND ANTISEPTIC-IMPREGNATED CENTRAL VENOUS CATHETERS IN INTENSIVE CARE PATIENTS

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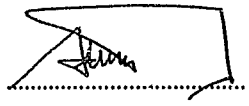
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in the branch of Microbiology

Johannesburg, 1999

DECLARATION:

I, Adriano Gianmaria Duse declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It had not been submitted before for any degree or examination at this or any other University. This work has not yet been presented at any scientific meeting, locally or internationally.



9th day of November, 1999

ABSTRACT:

The most frequent life-threatening complication of central venous catheters (CVCs) is septicaemia. Most CVC-related septicaemias derive from invasion of the catheter wound by microorganisms from the patient's own cutaneous microflora. To decrease the rates of CVC related sepsis, it has been the practice of many intensive care units to re-site CVCs at specified intervals (e.g., every seven days). However, there is good evidence to suggest that CVCs should remain in place until there is a clinical indication (e.g., fever without a known source) for change. In recent years, antiseptic- and antibiotic- impregnated catheters have been studied to determine whether they substantially reduce the incidence of catheter-related infection, extend the time that CVCs can be left in place safely, and are, overall, cost-effective.

The purpose of this study was to compare standard CVCs (ARROW Standard Triple Lumen catheter, Arrow International, Inc., Reading, Pa, US) with chlorhexidine gluconate/silver sulfadiazine-impregnated CVCs (ARROWgard™ Triple Lumen Catheter, Arrow International, Inc., Reading, Pa, US) left *in situ* for 14 days in adult intensive care unit (ICU) patients. Clinical data were collected and microbiological analyses were performed to determine the following: 1) the epidemiology of CVC-related infections (CRIs) in the General Intensive Care Unit, Johannesburg Hospital; 2) whether the use of antiseptic-impregnated (ARROWgard) catheters can significantly decrease the incidence of catheter-related infection as compared to the

ARROW Standard CVC at 14 days; and 3) whether the duration of catheter insertion can be safely increased to 14 days.

This is the first study conducted in South Africa documenting the epidemiology and rates of CVC-related infections (expressed per 1000 CVC days) in ICU patients, using the synthesis of both clinical and microbiological definitions as proposed by the Centers for Disease Control and Prevention (CDC), US. The General ICU of the Johannesburg Hospital is a multidisciplinary unit that admits trauma, medical, gynaecology and surgical patients.

Of the original sample of 149 patients receiving CVCs, only 118 CVCs were evaluable. Sixty-two patients received ARROW Standard CVCs and 56 received ARROWgard ™ CVCs. Data presented in this report on the types of colonising organisms (predominantly skin colonisers) and those causing infections via the transcutaneous route are consistent with those described in other studies. The routes of catheter infection in our patients, viz., mainly transcutaneous and the catheter hub, are likewise well documented in the literature. Molecular techniques (macro-restriction analysis using PFGE) were found to be useful in elucidating the aetiological role of coagulase-negative staphylococci in CRIs.

There was no statistically significant difference in total bloodstream infection rates between the group of patients who received ARROW Standard catheters (14.1 CRBs/1000 CVC days) and those who received ARROWgard catheters (10.8 CRBs/ 1000 CVC days). If only primary bloodstream infections are considered (i.e., excluding haematogenous seeding of the CVC) there is still no statistically significant

difference in CRI rates between the 2 catheter groups (12.7 CRIs/1000 CVC days and 8.1 CRIs/1000 CVC days for the ARROW Standard and ARROWgard ™ CVCs respectively). It is pertinent to note that the absence of statistical significance between the 2 groups was noted despite the fact that the ARROW Standard CVC group included more than double the number of trauma patients than the ARROWgard ™ group (20/62 [69%] versus 9/56 [31%] respectively). Furthermore, all patients with an additional intravascular catheter other than a CVC (6/118 [5.1%]) all belonged to the ARROW Standard group. Trauma patients as well as patients with other intravascular devices are, for obvious reasons, more likely to be susceptible to CRIs. Statistical analyses showed, in this study, that it was significant that more than double the number of trauma patients ($p = 0.04$) and all patients with other intravascular devices ($p = 0.016$) belonged to the ARROW Standard group with no apparent difference in infection rates in the 2 groups.

The mean duration of catheter placement for the full sample of 118 CVCs was 12.31 days. The relatively high rates of CRIs documented in our ICU should caution practitioners against leaving catheters *in situ* for periods longer than absolutely necessary. Further studies carried out in multi-disciplinary ICUs are required to determine an acceptable range of sepsis rates in this setting. Such studies should also investigate the optimal duration of CVC placement.

This study adds to the growing body of literature that suggests that chlorhexidine gluconate/silver sulfadiazine-impregnated CVCs are marginally, if at all, more effective than standard catheters in reducing CRIs. Until such time that more data become available to confirm or refute the anti-infective benefits, and therefore the

cost-effectiveness, of chlorhexidine gluconate /silver-sulfadiazine impregnated CVCs, it seems reasonable to reduce CRIs by concentrating on meticulous infection control practice.

ACKNOWLEDGEMENTS:

I wish to acknowledge and thank the following people who have contributed, directly or indirectly, to this research report and without whose input this work would not have been possible:

Arrow Africa (Pty) Ltd for gratuitous provision of the ARROW Standard and ARROWgard™ triple lumen central venous catheters used in this trial and for partial financial assistance for this study and the SAIMR for providing the balance of the funding that was required;

My Supervisor, Professor K P Klugman, Director of the South African Institute for Medical Research (SAIMR) and Chairman of the Wits School of Pathology, to whom I owe a very special debt of gratitude for his encouragement, invaluable assistance and criticism;

Professor R A Smego, Head of the Department of Clinical Microbiology and Infectious Diseases, SAIMR and Wits School of Pathology, for his ongoing support and for agreeing to act as Co-supervisor;

Professor H J Koornhof, Emeritus Professor and Consultant, Department of Clinical Microbiology and Infectious Diseases, SAIMR and Wits School of Pathology, for his mentorship over many years and for his meticulous scrutiny of this report;

Dr L Liebowitz, Head of the Microbiology Laboratory of the SAIMR, Johannesburg Hospital, for kindly assigning this project to me;

Professor G Richards, Dr M Mer, Ms M Lawrence, Ms S Murphy and all the Staff of the General Intensive Care Unit (Ward 576), Johannesburg Hospital, for their

invaluable cooperation throughout this study and for their involvement in all clinical aspects of this project;

Dr H Ye and Ms G Leong, STD National Reference Centre, SAIMR, for their assistance with setting up all the data collection sheets on EpiInfo (version 6.02);

Dr J Galpin, Senior Lecturer, Department of Statistics and Actuarial Science, University of the Witwatersrand, for her expertise in the statistical analysis of all data and for generously devoting so much of her time to this project;

Mr Wim van Nierop, Chief Scientist, Division of Hospital Epidemiology and Infection Control, SAIMR and Wits School of Pathology, for his ongoing assistance and for his expertise in molecular typing of the coagulase-negative staphylococci;

All the Medical Technologists in the Microbiology Laboratory, Johannesburg Hospital, and in the Division of Hospital Epidemiology and Infection Control, SAIMR and Wits School of Pathology, for the many hours of hard work they put into this project;

Mrs L Battaglia, Chief Librarian, SAIMR Library, Ms K Goosen and Staff for their untiring assistance in tracing books and journal articles;

Mrs M Britz, for the best secretarial support a person could wish to have;

finally, and by no means least, to my wife, Glynis, who has had to contend with so much while I was immersed in my work.

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INTRODUCTION AND REVIEW OF THE LITERATURE:

Central venous catheters (CVCs) are widely used in clinical practice for the administration of drugs, parenteral nutrition, haemodynamic monitoring, and fluid replacement. Unfortunately, infusion therapy has substantial and generally underestimated potential for producing iatrogenic disease, ranging from localised infection to thrombophlebitis to septicaemia, either originating from the percutaneous device used for vascular access or from contamination of the infusate administered through the device. Nosocomial intravascular device-related bacteraemia or candidaemia is associated with a 12% to 28% attributable mortality (Maki & Mermel, 1998).

To place this in context, a European multi-centre study published in 1983, showed that of 10 000 surgical patients 63% had intravascular devices (Nystrom, Olensen-Larsen, Dankert et al., 1983). Bacteraemia occurred in 4.48% of subjects with central venous catheters, 6.37% with peripheral venous catheters, whilst only 0.05% of patients without intravascular access developed nosocomial bacteraemia. Thrombophlebitis occurred at a rate of 10.3%. More recently, the number of cases of catheter-related bacteraemias (CRBs) reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre (PHLS-CDSC) in England and Wales increased by 39% between 1989 and 1991, with nearly 4000 bacteraemias reported in 1991 (Elliott, 1993). Subsequent to this period there was a gradual increase in CRBs, with approximately 5000 cases reported in 1995 (Elliott & Tebbs, 1998). This increase may partly reflect the greater use of catheters and a heightened clinical awareness of associated infections, and it is likely that many cases remain

undiagnosed, putting the annual figure of CRBs in England and Wales in the region of 10 000 patient-episodes (Elliott & Tebbs, 1998).

Approximately 150 million intravascular devices are purchased each year by hospitals and clinics in the United States, 5 million of which are central venous catheters (Sitges-Serra, Pi-Suner, & Garces et al., 1995). In the US, more than 50% of hospitalised patients have an intravascular catheter in place, clearly placing a large number of patients at risk for catheter-related infection (CRI). It is estimated that approximately 850 000 CRIs occur annually with 50 000 CRB associated with an attributable mortality of 14-28% and resulting in 7 000 to 14 000 deaths (Widmer 1997:184). Although several guidelines exist for catheter insertion and care, CRB continues to be a major problem mainly because of the high-risk nature of the patient population requiring prolonged central venous access. Given the morbidity, mortality, and cost associated with nosocomial bacteraemia, effective strategies to reduce the rate of CRIs should become a high priority in infection control practice.

Microbiology of CVC-related infections:

Because the majority of microorganisms that cause CRIs are derived from the skin, it is not surprising that staphylococci, which constitute a large component of the cutaneous microflora, are the most frequently isolated pathogens. Coagulase-negative staphylococci (CoNS) account for approximately 30-40% of the isolated pathogens, and 60% of these are *S epidermidis* (Widmer, 1993:560).

Clinical evidence for of catheter sepsis includes inflammation, with or without a purulent discharge at the insertion site. Evidence of systemic infection and, occasionally, metastatic sepsis at other sites may be present. Endocarditis is always a concern with infected centrally-placed vascular catheters. However, positive cultures for CoNS isolated from catheter and peripheral blood cultures are not conclusive in diagnosing CRB. Discriminatory typing techniques are necessary to prove the relatedness of strains (Mermel, McCormick & Springman et al., 1991). It is important to acknowledge, however, the polyclonality of strains within a species of microorganisms that form part of a bacterial biofilm. Unless several colonies displaying different colony morphologies are tested, using highly discriminatory molecular typing techniques, it may be difficult to elucidate the aetiological importance of a microorganism in CRIs. Most of the studies performed in the 1970s and 1980s did not employ such techniques and may have misclassified episodes of CRB when, in fact, two different, unrelated strains were present (Widmer, Nettleman & Flint et al., 1992).

Staphylococci, including CoNS, produce variable amounts of capsular material. External to the cell capsule is extracellular slime material produced under certain circumstances of growth (Bayston & Rodgers, 1990). The glycocalyx encompasses both capsular and extracellular slime material that forms a biofilm within which the microorganisms grow. Extracellular slime production appears to occur more readily, but not universally, with certain strains of *S epidermidis* associated with foreign bodies and, in particular, indwelling medical devices. Because CoNS are important skin commensals and frequent contaminants in clinical specimens, many investigators have attempted to differentiate pathogens from contaminants by correlating

production of extracellular slime by CoNS with pathogenicity. The function of slime has been much debated but it is believed to act as an ion exchange resin for nutritional purposes. Bacterial growth within a biofilm differs markedly from the planktonic state and has been extensively studied in recent years. Biofilm-associated CoNS appear to be protected in several ways. For instance, slime from CoNS has been shown to have a number of immunomodulatory effects (Gray, 1984; Johnson, 1986; Dinarello, 1989; Noble, 1990; Stout, 1992; Shiro, 1994). Whilst these phenomena are of interest, they do not clarify the exact molecular and genetic nature whereby slime production is inhibitory to host defences.

Chemical analysis of slime indicates that it is a glycoconjugate composed of glycerol phosphate, d-alanine, N-acetylglucosamine and usually glucose (Kotilainen, 1990; Hussain, 1991). Slime production is strain-variable and affected by circumstances of growth (Hussain, Wilcox & White, et al., 1992a). Class I and II phenotypes of CoNS have been described (Barker, Simpson & Christensen, 1990). The former phenotypes demonstrate good slime production under aerobic conditions but not in anaerobic states, whereas class II phenotypes produce little/no slime under either condition. Slime production has been measured qualitatively and quantitatively. The Congo red agar test has been used widely for individual colony testing, and radiochemical analyses have also been described (Hussain, Collins & Hastings et al., 1992b).

Studies of device-associated infections have focused have generally, but not universally, shown slime production by *S epidermidis* to be linked with pathogenic potential in relation to device-associated infections. Despite some correlation between slime production and clinical significance (Christensen, 1982a; Christensen, 1982b),

the likelihood of an infecting strain being a slime producer varies markedly. Although slime production may be used as one of several markers to determine the clinical significance of an isolate, testing for this property is not accurate enough to differentiate between infecting and non-infecting strains in a clinical situation. For this reason, it was decided not to test for slime production by CoNS recovered in this research report.

Although CoNS are the commonest organisms cultured from intravascular catheters, they do not cause bacteraemia as often as *Staphylococcus aureus* (Richet, Hubert & Nitemberg et al., 1990). *S aureus* accounts for approximately 5%-10% of CRIs. Catheter-related bacteraemia caused by *S aureus* is a serious infection with complications such as septic thrombophlebitis, endocarditis and osteomyelitis occurring in up to 22% of patients (Richet et al., 1990). A catheter culture positive for *S aureus* in a patient receiving total parenteral nutrition is strongly predictive of a CRB. Furthermore, in HIV/AIDS patients, it would appear as if *S aureus* has superseded the CoNS as the most important cause of CRIs (Widmer, 1993:560; Sweed, 1995). Enterococci account for 4%-6% of CRI isolates. *Corynebacterium jeikeium* is also found on the skin and has emerged, in recent years, as an important cause of intravascular device-related sepsis, especially in immunocompromised patients (Brown, 1995:1876).

The isolation of Gram-negative bacteria, which are a less frequent cause of CRIs, may be more alarming. Gram-negatives may constitute up to 13% of all CRI isolates. In the absence of infection from another clinical site, isolation of these organisms from cultures from patients with suspected CRIs, should alert the clinician to the possibility

of contamination of parenterally-administered infusates, a contaminated in-use disinfectant solution, or infection of arterial transducer systems in intensive care units (ICUs) (Widmer, 1993:560).

Candida species are becoming more frequent causes of CRI, accounting for 2-5% of all isolates (Widmer, 1993: 560). *Candida* spp., *S aureus,* and *Malassezia furfur* are of particular concern in patients in neonatal ICUs in patients receiving total parenteral nutrition (TPN).

Pathogenesis of CVC-related infections:

In most cases of catheter-related bloodstream infection colonisation of the catheter precedes the systemic infection. Microorganisms multiply either on the external surface of the catheter (extraluminal colonisation), and subsequently dislodge, causing episodes of bacteraemia, or they gain access to the bloodstream via the hubs and/or through the internal lumen. Maki (1994), identifies the patient's skin as the prime portal of colonisation, and organisms at the insertion site originate from the patient's own flora, the hands of health care workers, or possibly from contaminated skin antiseptics.

In a study of surgical patients receiving short-term TPN, Linares et al. (1985) showed that the hub was a more significant source of infection than the skin. Other implicated routes of CRI include haematogenous seeding from a distant focus of infection or, infrequently, via infusion of a contaminated fluid. Another mechanism of catheter colonisation is through contamination of the device during its insertion with

subsequent multiplication of bacteria multiply upon the catheter surface. Evidence supporting this route of catheter contamination comes from a study by Raad et al. (1994), which found that by optimising aseptic technique for insertion of catheters, a six-fold reduction in CRB infection was possible.

Short-term intravascular catheters (average duration $\leq$ 8 days) are colonised predominantly from the skin (75%-90%), followed by the hub/lumen (10%-15%), the bloodstream (3%-10%), and infusates (2%-3%) (Maki, 1988; Flowers, 1989; Mermel, 1991). For catheters that are placed for periods exceeding 8 days, the relative frequencies of these sources of catheter colonisation are less certain, mainly because removal of many long-term catheters is routine, and not related to infection. Data for both short- and long-term catheters are available comparing the skin versus the catheter hub as sources of CRB. Careful analysis of 7 studies (Sherertz, 1997:4) reveals that for short-term catheters the skin is more likely than the hub/lumen to be the source of CRB (92% versus 42%), whereas with longer-term catheters (*in situ* from 20-115 days) the hub/lumen is the more likely source (66% versus 26%). These findings are supported by Raad et al. (1993), who showed that the quantity of biofilm on the internal surface of the catheter was less than the external surface during the first 10 days of catheterisation; thereafter, it steadily increased until it equalled or exceeded the biofilm on the external surface. More recently, Elliott et al. (1997) demonstrated that microorganisms could also be impacted onto the catheter's distal tip at the time of insertion, despite careful aseptic technique and meticulous skin preparation. Furthermore, microorganisms may also contaminate other items such as the insertion cannula, guidewire, and dilator. Interestingly, protection of catheters via a Schwan sheath upon insertion through the skin may reduce contamination (Elliott & Tebbs,

1998). This has important implications for the practice of replacing catheters over the same guidewire.

Efforts to prevent intravascular catheter-related sepsis have been primarily directed towards minimising the access of microorganisms to the device surface. This approach focuses on two main areas: (1) sound infection control practice and patient care, and (2) development of new catheters. The remainder of this discussion focuses on the latter.

For many years, the goal of polymer scientists and microbiologists has been to manufacture a CVC that will inherently inhibit bacterial colonisation and subsequent growth on the catheter surface. There are several approaches to production of such an anti-infective catheter currently under consideration. Firstly, polymers with anti-adherent properties have been developed which are produced via modification using chemical, radiation or glow discharge methods (Jansen, 1993). Polyurethane catheters coated with hydromer have an ultra-smooth surface and are less likely to be colonised with microorganisms as compared with uncoated catheters (Tebbs & Elliott, 1994). However, despite these improvements to catheter materials infections still arise. Secondly, antimicrobial agents (antiseptics, antibiotics, and metallic ions) have been coated onto or incorporated into the catheter material (Tebbs & Elliott, 1994). CVCs coated with both hydromer and teicoplanin (Hydrocath®, Ohmeda, Swindon, UK) have been evaluated by Bach, et al. (1994). These investigators found, in a prospective randomised pilot study in patients undergoing major abdominal surgery, that approximately 75% of the initial teicoplanin coating was released after the first day of catheterisation, and after 36 hours no antibiotic was retained. No differences were

subsequently detected in the degree of bacterial colonisation between the teicoplanin-coated CVCs versus the uncoated, control CVCs. Thirdly, the application of low amperage electrical current to catheters, perhaps in combination with an antimicrobial, offers a novel method for protection from CVC-related sepsis (Blenkisopp, 1992; Costerton, 1994; Jass, 1995; Liu, 1997). Bacteria are relatively negatively charged as a consequence of the physicochemical properties of their cell wall. By applying a constant current to carbon impregnated catheters, prevention or reduction of microbial colonisation of these devices can be achieved by repulsion (Liu, Tebbs & Byrne et al., 1993). It has also been shown that electrical current has antimicrobial activity as a consequence of the production of hydrogen peroxide and free chlorine formed by electrolysis at the catheter surface (Liu, Brown & Elliott, 1997). Furthermore, electrical current can enhance the activity of antimicrobials that are administered concomitantly (Costerton, 1994; Jass, 1995). The use of electricity is an attractive alternative in that it avoids problems associated with antimicrobial resistance. Furthermore, this technology may offer long-term protection from infection of not only intravascular catheters, but of other prosthetic devices as well.

Several risk factors have been described that contribute to the development of catheter-related sepsis (Maki & Mermel, 1998). These include: the patient's underlying clinical condition, catheter material, catheter size, site of insertion; insertion technique and subsequent maintenance, manipulations, infusions, and insertion time. The duration of catheterisation has always been considered one of the most important factors that influence the development of catheter-related sepsis. The precise role of duration of catheterisation in the pathogenesis of catheter-related infection is controversial. In the adult intensive care unit of the Johannesburg Hospital

the policy is to routinely re-site CVCs every seven days. However, Cobb et al. (1992), suggest that unless there is clinical evidence of catheter-related sepsis (e.g., local signs of inflammation and infection; pyrexia without an attributable source), CVCs should remain in place and need not be routinely replaced. Furthermore, there are several references in the literature that suggest that CVCs that are impregnated with antimicrobial substances can reduce the incidence of catheter-related infection and extend the time that CVCs can be left in place safely (Clemence, 1993; Maki 1997, Darouiche 1999). In doing so, antimicrobial-impregnated catheters may prove cost-effective (Wenzel & Edmond, 1999).

The ARROWgard™ triple-lumen catheter is of polyurethane material impregnated with two antimicrobial agents, chlorhexidine and silver sulfadiazine. Both agents, either singly or in combination, have been shown to be efficacious in a variety of clinical settings. Chlorhexidine has been used for more than three decades as a skin disinfectant without evidence of irritation or sensitisation, has been used as a mouth rinse for control of dental plaque, and as a surgical wound and bladder irrigant. The combination of silver sulfadiazine and chlorhexidine has been shown to have a synergistic antibacterial effect (Modak & Sampath, 1992). The probable mechanism of action for this synergism is chlorhexidine effect on bacterial cell wall permeability by altering the bacterial cell membrane, permitting the entry of silver ions that bind to the cell's DNA helix and thereby preventing replication. In order to address concerns from clinicians about the toxicology and safety of chlorhexidine and silver sulfadiazine released from the catheter, Farber (1992) reviewed the toxicological safety of the agents (silver, sulfadiazine and chlorhexidine individually, and in combination). Although hypersensitivity reactions have been recognised to occur

when patients are exposed to silver, sulfadiazine and chlorhexidine, only minute quantities of these agents are released from the antiseptic catheter. The potential exposure of patients to these agents via the antiseptic catheter is less than one thousandth of that encountered when these compounds are used on burn wounds, on cutaneous wounds or as mucosal irrigants. Thus, the possibility of toxic reactions occurring through the use of the catheter alone is extremely remote. Hypersensitivity reactions to silver are rare and are associated with long durations of exposure at levels considerably higher (> 60 μg/dl of blood) than those released by the antiseptic catheter (where highest level of silver found was 7.3 μg/dl of blood). Hypersensitivity reactions to sulfadiazine are seen in 1-2% of patients. The most common expressions of sulphonamide hypersensitivity include vascular lesions, drug fever, serum sickness, anaphylactoid-type reactions and skin lesions including Stevens-Johnson syndrome and erythema multiforme (Mandell & Sande, 1980). Topical application of sulphonamides is most likely to produce a hypersensitivity reaction (De Swarte, 1986). Sulphonamide sensitivity reactions are least likely to develop if the daily dose of sulphonamide is below 2 grams or blood levels are below 5000 μg/dl. According to Farber (1992), the level of sulfadiazine in the blood of a catheterised patient could not exceed 8 μg/dl even if all the sulfadiazine in the catheter was released at once and distribution of sulfadiazine to other body compartments did not occur. There is, therefore, no practical likelihood that patients would be sensitive to the minute levels of exposure of sulfadiazine from the catheter. Furthermore, no toxicological adverse effects have been noted in patients who have had the antiseptic catheter *in situ* who were sensitive to sulphonamides but unaware of their sensitivity. Finally, hypersensitivity reactions to chlorhexidine are uncommon and are associated with

much higher levels of exposure (10 000 μg/dl) than is likely to be seen through the release of chlorhexidine from the catheter (which, maximally, may be 21.5 μg/dl). Despite these claims, however, a recent report from Japan described 12 patients who developed anaphylactic shock whilst a chlorhexidine/ silver sulfadiazine-impregnated catheter was *in situ* (quoted in Elliott & Tebbs, 1998:196). It was postulated that reactivity to the catheters might have been related to prior exposure to higher concentrations of chlorhexidine in skin creams. Clearly, the potential for toxicity of antibacterial substances used to coat catheters is of concern, and ongoing surveillance and reporting of such events must be given high priority.

Diagnosis of CVC-related infections:

The diagnosis of CRI and CRB remains problematic. Many intravascular device-associated infections are either undiagnosed or only become recognised once catheters become colonised and bacteraemia is detected. Clinical clues such as the presence of erythema, oedema, purulence, and pain at the catheter insertion site may be helpful in the diagnosis of peripheral intravascular device-related infections, but are rarely seen in patients with established CRIs (Pittet, Chuard & Rae et al., 1991). It is important to note that phlebitis associated with peripheral catheters is more frequently a physicochemical phenomenon rather than an infective process caused by bacteria.

Successful treatment of serious CRIs is dependent on early diagnosis. In view of the fact that clinical markers show a very poor correlation with infections associated with CVCs, laboratory tests are important to confirm a clinically suspected diagnosis of CRI. The tests can be divided into two categories: those that require removal of the

CVC for microbiological diagnosis, and those that can be performed leaving the CVC *in situ.* Clearly, diagnostic approaches requiring the removal of the CVC provide a retrospective diagnosis, and may not always be valuable in the clinical management of such patients. In more than 70% of episodes of suspected CRI or CRB, fever can be attributed to a different source, and the catheter in unnecessarily removed and replaced (Widmer, 1997).

Qualitative culture of the catheter in which the segment is incubated in liquid medium is a sensitive technique for diagnosis of infection but provides no information about the number of microorganisms present; the presence of a single contaminating organism can lead to a positive culture. In an effort to improve the specificity of catheter cultures, quantitative techniques have been developed that demonstrate sensitivity comparable to that of broth culture but with superior specificity and predictive value. Detection of catheter-related infections is also possible by microscopic examination of catheter surfaces following Gram- (Cooper & Hopkins, 1985) or acridine orange- (Zufferey, Rime & Francioli et al., 1988) staining. This allows rapid detection, preliminary characterisation, and quantitation of the organisms present. Although these staining techniques show promise, they are not feasible for all types of catheters and are technically quite demanding and labour intensive.

In 1977, Maki et al. (1977), developed a roll-plate semiquantitative culture (SQC) technique in which a segment of the removed catheter is rolled back and forth across the surface of a blood agar plate. Colonies are counted after incubation and the presence of $\geq$ 15 of the same species indicate colonisation. Because the technique samples only the exterior portion of the catheter, it may not detect infections

originating in the lumen of the catheter. It has been suggested that colonisation of the lumen may be an important reservoir of infection in some catheter infections. Cleri et al. (1980) developed a quantitative technique in which the removed catheter lumen is flushed with liquid medium and agitated vigorously to dislodge adherent microorganisms. The subsequent suspension is then serially diluted and plated. The presence of > 1000 cfu/ml suggests the presence of bacteraemia. The theoretical advantage of this approach is that both the interior and exterior surfaces of the catheter are sampled. A modified procedure has been recommended by Rello et al. (1989), who suggest using both the semiquantitative culture of the exterior catheter surface and the quantitative culture of the lumen to increase the detection of catheter colonisation. Because some organisms adhere avidly to catheter surfaces, Sherertz et al. (1990), have used sonication (catheter segments are placed into 10 ml broth for and subjected to 55,000 Hz, 125W for 1 minute) followed by vortexing for 15 seconds before performing quantitative cultures to remove sessile adherent organisms deeply embedded in the biofilm layer. The roll-plate technique remains the most frequently used test to determine extraluminal bacterial colonisation of short-term intravascular catheters.

Some important findings have emerged in studying the ultrastructure of indwelling vascular catheters with scanning and transmission electron microscopy and comparing the results with the results of the semiquantitative roll-plate technique and culture after sonication. Raad et al. (1993) showed that external colonisation was predominant in the first 10 days of catheter placement, while intraluminal colonisation became predominant after 30 days. These findings suggest that the semiquantitative roll-plate technique is most useful for short-term catheters, as indeed was the case for most of

the catheters in the original study by Maki et al. (1977), whereas for long-term catheters intraluminal cultures should be performed. Ideally, although this may not always be practical, both extra- and intraluminal surfaces of CVCs should be cultured.

Accurate diagnosis of device-related infection can be difficult, since true infection must be distinguished from colonisation. When CVC-related infection is suspected, the intravascular catheter should be removed and 2-3 cm segments from both the distal tip and transcutaneous portions should be submitted for culture. The clinical microbiology laboratory must be able to identify and quantitate the microorganisms present.

Full diagnosis can be made by the culture of peripheral and catheter-drawn blood samples. Although it is not common to use a quantitative culture technique when CVCs are left in place, this procedure could be recommended, particularly where temporary withdrawal of the catheter would be life-threatening.

Table 1 summarizes different laboratory tests, as well as their limitations, which can be performed to diagnose CVC-related infections. (Adapted in tabular form from information contained in Kristinsson, 1997).

Table 1. Laboratory tests used in the diagnosis of intravascular device-related infections.

Laboratory test	Comments
Tests which require removal of CVC:	
Broth cultures	1. Qualitative test 2. More sensitive than SQC, but much less specific 3. Very low positive predictive value; however, when broth cultures are negative, however, probability of CRI is low 4. Because are poor predictors of catheter colonisation and CRI, they should never been used alone. In most centres, this technique has been replaced by SQC or quantitative cultures
Semiquantitative roll-plate technique (SQC)	1. Standard method for culturing intravascular devices – in original study methodology derived largely (74%) from short peripheral venous catheters 2. Detects organisms on extraluminal CVC surface only 3. Low positive predictive values (ranging from 9% to 44%) reported. Positive predictive value may be increased when catheters remain in place for long periods
Staining and direct microscopy of catheter surface	1. Gram staining; acridine orange staining of catheter segments 2. Cumbersome, time-consuming 3. Lack of sensitivity 4. Offers no advantage over culture
Flushing Vortexing Sonication of tip, followed by quantitative culture	In a study (Kristinsson, Burnett, & Spencer, 1989) where SQC and quantitative intraluminal cultures were performed together with culture after ultrasonication, the ultrasonication did not increase the sensitivity of the cultures. A threshold of 100CFU and quantitative intraluminal cultures of the catheters were the best predictors of infection.
Tests which can be performed leaving the CVC *in situ*:	
Intraluminal culture	1. Sampling performed by intraluminal insertion and rotation of a plastic obturator (guidewire) or endoluminal brush 2. Method relatively easy; if cultures are done serially specificity is retained but sensitivity compromised 3. Value of technique in predicting CRB not assessed 4. Potential cause of bacteraemia consequent to dislodging intraluminal biofilm-embedded organisms during the procedure
Hub cultures	1. Based on assumption that infection is likely to have originated from the hub. Is therefore more appropriate for long-term (especially tunnelled) CVCs 2. Useful in predicting CRB, but should preferably be used in conjunction with skin/exit site cultures 3. Sensitivity of hub cultures can be increased from 80% to 90% by combining them with results of skin/exit site cultures 4. There is a high association between SQC and superficial cultures of the skin and hub (predictive value positive and negative for CRI 66.2% and 96.7% respectively, prevalence 38.1%) 5. Negative skin/exit site cultures have a high negative predictive value
Quantitative blood cultures simultaneously drawn through catheter and a peripheral vein	1. Basically 3 methods employed for quantitation of blood cultures: pour plate method, lysis centrifugation tubes (Isolator; Du Pont Co.), direct inoculation of blood onto agar media 2. Using a colony count fourfold higher in blood drawn through catheter than in simultaneously drawn peripheral blood as a cut-off value associated with sensitivity of 94%, specificity of 100%, and a positive predictive value of 100% 3. Useful test, but with practical difficulties
Other tests:	
Skin insertion site cultures + blood cultures yielding same organism	When CVC is suspected to be infected, but insertion of a new catheter is problematic, attempt to predict likelihood of infection to avoid unnecessary removal by quantitative blood cultures taken through catheter and from a peripheral vein. If exit site looks infected, exit site cultures should be performed. Cultures from exit site/surrounding skin are not useful on their own if there is no evidence of exit site infection. They should therefore be used as an adjunct to other cultures.

Unfortunately, a gold standard for the laboratory confirmation of CRI remains to be found. Clinicians should, therefore, be aware of the limitations of the techniques used by the microbiology laboratory. Because both clinical and laboratory diagnoses are imprecise, it is only through careful synthesis of both sources of information that a more reliable and correlated diagnosis can be reached. Perhaps, more importantly, the practical value of CVC cultures in patient care should be considered. A study looking at the routine use of the SQC technique defined clinical impact as a change in diagnosis or therapy on the basis of the culture result (Widmer, Nettleman & Flint, 1992). For 96% of the 157 catheter cultures there was no impact. Careful selection of culture methods, and good liaison between clinicians and laboratory personnel are likely to increase the impact. It will also be necessary to define which patient population is most likely to benefit from such cultures. Clearly, from an infection control perspective, routine cultures (SQC and/or quantitative) may be useful to record device-related infection rates. Such information serves as an important tool to measure the quality of CVC care.

MATERIALS AND METHODS:

Study Design and Population:

The study was prospective and double-blind in design. In order to determine whether antiseptic-impregnated catheters left in situ for 14 days had significantly lower rates of sepsis than standard catheters left in situ for the same period (confidence interval 95%; power 80%; equal numbers of patients in each group [ratio 1:1]; relative risk 4) a minimal sample size of 176 patients was required. However, unexpected termination of funding precluded us from reaching this target. The study cohort, therefore, consisted of 149 patients requiring insertion of a CVC who were consecutively assigned to receive either the ARROW Standard (non-antiseptic coated) triple-lumen CVC or the ARROWgard™ antiseptic catheter which is impregnated with chlorhexidine gluconate and silver sulfadiazine. The catheter manufacturer (Arrow International, Inc., Reading, Pa, US) ensured that CVC catheter consignments consisted of equal numbers of ARROW Standard and ARROWgard™ triple-lumen CVCs which could not be differentiated from each other except for a numeric code (5592/5593) which was broken only upon completion of the study. All the patients in the study were admitted to the General Intensive Care Unit (Ward 576) of the Johannesburg Hospital (Ga teng, South Africa) and consisted of a mix of patients who were referred for intensive care from gynaecological, surgical, trauma and medical services. Of the original cohort of 149 patients, 31 were excluded from the study either because they demised before blood cultures could be drawn, or because the microbiology laboratory received incomplete sets of specimens for processing, or because of lack of certain components of critical data, such as whether the catheter

was coded 5592 (uncoated) or 5593 (coated), were omitted from patient records. Consequently, it was not possible to analyse or determine whether there were any differences in the 31 exclusions between the 2 groups (5592/5593). Criteria for inclusion to the study included: age greater than 18 years, a white blood cell count on admission > $4X10^9$/l, absence of skin burns, no history of allergy to sulpha-containing preparations, and patient consent.

Catheter insertion:

After washing hands, donning sterile gowns and gloves inserted the catheters were inserted by trained Registrars or Consultants working in the unit. The catheters were inserted into various sites, predominantly left or right internal jugular vein or left or right subclavian vein, as judged most convenient by clinical evaluation. Subanalyses of colonisation and infection rates according to site of insertion were performed. Patients who had previous central venous catheters or who had other catheters such as arterial lines, etc. were not excluded from the study sample. All existing intravascular catheters were removed prior to the insertion of the ARROW Standard/ARROWgard CVCs. Study catheters were not exchanged over guidewires. Maximal sterile barrier precautions were taken, including use of sterile gowns, sterile gloves, full sterile drapes, masks, and caps. At the time of catheter insertion, the skin insertion site was cleansed with 0.5% chlorhexidine gluconate in 70% alcohol. In each case the preparation was applied to the skin for two minutes before catheter insertion. The insertion site was then covered with Micropore® dressings. The insertion site was inspected daily for evidence of infection such as erythema, purulence, swelling or tenderness over the catheter.

For each patient the following data were collected: age; sex; underlying disease; history of intravenous drug abuse; duration of hospitalisation prior to catheter insertion; CVC insertion site; insertion technique; date of insertion and removal; indication for CVC; number of catheter manipulations; antibiotics received; presence of other intravascular lines; and white blood cell count and temperature at time of catheter-related sepsis and catheter removal. In patients with CVC-related sepsis, we also analysed the interval between catheter insertion and the detection of sepsis, the aetiological agents, the management of the infection (antibiotics, catheter removal), and the outcome. Follow-up began at the time of insertion and ended when the CVC was removed or when death occurred. Indications for catheter removal included end of treatment, suspected CVC infection, and major mechanical problems such as kinking, obstruction, or leaking. During follow-up, the following information was obtained for all patients: site of catheter insertion; dates of catheter placement and removal; occurrence of complications or breaches in aseptic technique during insertion or removal; reason for using the catheter (intravenous administration of drugs, including antibiotics; administration of total parenteral nutrition [TPN]; haemodynamic monitoring; administration of blood products; or a combination of these reasons); type of dressing; and reason for catheter removal. In addition, clinical data obtained included: neutrophil and platelet counts; presence or absence of fever and infection; and other therapeutic interventions (e.g., ventilation) that were performed during the period of catheterisation. The catheter remained in place until it was no longer needed, until a specific event necessitated its removal, or for 14 days, whichever occurred first.

Definitions:

The Centers for Disease Control and Prevention (CDC) developed a guideline in 1996 for the prevention of intravascular device-related infections (Centers for Disease Control Working Group, 1981). Current definitions and terminology applied to CRIs are based on this guideline and may vary depending on the type of catheter (e.g., peripheral catheter, short-term catheter, or long-term catheter).

For the purposes of this study, the following definitions for short-term CVCs were applied:

1. Colonised catheter: growth of $\geq$15 colony forming units (CFUs) by the roll-plate technique or $\geq 10^3$ CFU (quantitative culture) from a proximal or distal catheter segment *in the absence of accompanying clinical symptoms.*
2 Catheter-related infection (CRI): growth of $\geq$15 colony forming units (CFUs) by the roll-plate technique *with accompanying signs of inflammation* (e.g., erythema, warmth, swelling, tenderness, purulence) *at the device insertion site.* Inflammation at the catheter site was defined as the presence of either lymphangitis or purulence or two or more of the following: erythema, tenderness, warmth, and thrombosis.
3. Catheter-related bloodstream infection (CRB): isolation of the same organism (identical species, same antimicrobial susceptibility profile) from a semiquantitative or quantitative culture of a catheter segment and from blood cultures (preferably collected from a peripheral vein) of a patient with accompanying clinical symptoms of CRB and no other apparent source of infection.

To identify the source of an isolate causing a CRB, the following definitions were applied:

1. Infusate-related sepsis was determined if the same organism was present in the infusate, CVC hubs, CVC distal segment (tip) and skin cultures were negative.
2. Hub-related sepsis was determined if the same organism was recovered from the CVC hub, the CVC distal segment, and blood cultures; culture/s of infusates were negative; skin cultures were either negative, or positive for different microorganisms.
3. Skin-related sepsis was determined if the same microorganism was isolated from the skin, the CVC transcutaneous segment, the CVC distal segment, and blood cultures; CVC hub cultures and culture of infusate/s were negative.
4. Haematogenous seeding of the catheter was determined if the same microorganism was isolated from blood cultures, the CVC distal segment, and a distant source of infection; cultures of infusate/s, CVC hubs and skin were negative.

Microbiological analyses:

Collection and processing of CVC pre-insertion and pre-removal specimens for quantitative culture of the skin insertion site:

Ten square centimetres of skin about the catheter site were sampled. A sterile template was applied to the site and the exposed area cultured with a sterile cotton-tipped

applicator pre-moistened with Stuart's transport medium by vigorously scrubbing the entire area four times, twice in one direction and twice more perpendicularly to the first [11]. In the laboratory the tip of the applicator was immersed in 1 ml of sterile saline and agitated vigorously on a Vortex mixer. Serial dilutions were inoculated onto blood agar plated (done in triplicate) and incubated aerobically at 35° C overnight. All colony types were enumerated using routine laboratory methods.

Collection and processing of specimens from the catheter hubs:

Catheter hubs were cultured aseptically inserting a smaller, sterile cotton-tipped applicator into the hub and, while exerting gentle axial pressure, rotating the applicator. The tips of each applicator were cultured in a fashion similar to the skin cultures.

Collection and processing of infusates:

A 10 ml sample of each infusate that was administered to the patient via the CVC was collected aseptically and sent to the laboratory in a sterile universal container. On receipt to the laboratory, the infusate was centrifuged and the deposit cultured onto a segment of a blood agar plate (incubated at 35° C for 72 hours) and in 10 ml of brain heart infusion broth and incubated at 35°C for 7 days before being terminally subcultured and discarded.

Collection and processing of blood cultures:

A set of blood cultures was obtained percutaneously and another through the catheter from patients with fever or other sites of infection or inflammation of the insertion site and through the catheter at the time of catheter removal. Each collected "set" of blood culture bottles consisted of an aerobic Bactec® bottle, an anaerobic Bactec® bottle, and a fungal blood culture tube collected from a single venepuncture site. Clinicians were advised to collect no less than 5 ml of blood in each (aerobic and anaerobic) Bactec® bottle. Blood cultures were processed for at 35°C for 7 days by the BACTEC-460® radiometric method. Fungal blood cultures were processed using conventional methods.

Collection and processing of catheter segments for culture:

To prevent contamination by skin organisms, the skin around the insertion site was cleaned with 0.5% chlorhexidine gluconate in 70% alcohol and allowed to dry prior to the removal of the cannula. Catheters were removed aseptically keeping the externalised portion directed upward and away from the skin surface to minimise contamination by skin organisms. Two portions of the catheter were submitted for bacteriological processing: the distal intravascular tip and the proximal transcutaneous segment. The segments were cut with a sterile scalpel and were 5 cm in length. The segments were sent to the laboratory in sterile universal containers and were cultured within 2 hours of collection to prevent desiccation of microorganisms. A semiquantitative culture was performed on the catheters using the method described by Maki, et al. (1977). Each catheter segment was rolled back and forth at least four times across the surface of a blood agar plate using flamed forceps. Subsequently, the

catheter segment was immersed in brain heart infusion (BHI) broth. Broth and plates were incubated at 35°C for 72 hours. All broths were subcultured onto blood agar plates. All colony types appearing on the primary plates were enumerated, and all organisms recovered from both plates and broths were id.. ified.

Identification of organisms:

Full identification of microorganisms was carried out to genus and species level using conventional methods. Antimicrobial susceptibility profiles were determined using the Kirby-Bauer disc diffusion test in accordance with NCCLS criteria (National Committee for Clinical Laboratory Standards, 1998).

Molecular tracking of CoNS isolates suspected to be implicated in CRI or CRB:

To confirm the diagnosis of catheter-related bloodstream infection, DNA molecular typing done using pulse-field gel electrophoresis was performed on organisms that were of the same species, had the same antibiogram, and were isolated from the catheter and the bloodstream during the period of catheterisation. Macro-restriction analysis was performed as previously published (Zaidi, Harrell & Rost, 1996) with some modifications. Briefly, 2 ml of organisms grown overnight in BHI broth were centrifuged and the cells resuspended in EET buffer (100 mM EDTA, 10 mM Tris-HCl pH 8). Agarose gel blocks were poured after adding an equal volume of 2% agarose in EET buffer to the suspended bacteria. Cell lysis was performed in 2 ml of EET buffer containing 10 µg/ml lysostaphin. at 30°C for 5 hours. The buffer was replaced with EET buffer containing 1 mg/ml Proteinase K and 1% SDS and

incubated overnight at 37°C with gentle shaking. Restriction digest was performed using SmaI at a concentration of 0.3 U/µl for 2 hours. PFGE was performed on the CHEF-DRII system (Biorad, Hercules, California) under the following conditions: 6 v/cm for 20 hours with switch times starting at 5 sec and ending at 50 sec. GTBE (45 mM Tris-Borate, pH 8.0; 1 mM EDTA; 100 mM glycine) was used as running buffer. Staining of the gel with ethidium bromide and viewing using an UV transilluminator followed PFGE. Isolates were designated as genetically indistinguishable (i.e. identical), closely related, possibly related or unrelated according to the criteria of Tenover et al (1995).

Statistical analyses:

The statistical analyses of data collected for this study was carried out with the expert assistance of Dr Jacky Galpin from the Department of Statistics and Actuarial Science, University of the Witwatersrand. Analyses of catheter-related colonisation and bloodstream infection included all patients who were enrolled in the study and had their catheters cultured by the Maki semiquantitative roll-plate technique. Testing was done using the chi-square contingency table test for yes/no data and the Wilcoxon-Mann-Whitney test for continuous data. The latter non-parametric test was used as many of the variables were skewed. All *p* values were based on two-tailed tests of significance. Similarly, in the results tables and discussion median and range rather than means are used throughout for continuous variables such as age, and total duration of catheterisation (in hours). Because of concerns of the possible skewness of data, the non-parametric Kruskal Wallis test was used to determine the means for the different organisms isolated from the pre-CVC-insertion skin swab and the pre- CVC-

removal skin swab, and to test if there were differences in log counts between the ARROW Standard and ARROWgard™ triple-lumen CVCs for each organism.

Role of industry:

Arrow International (Reading, Pa, US) provided the catheters, and limited funding for this study totalling R 10 000. Arrow International was not (directly or indirectly) involved in the design of the study, collection or analysis of data, or the decision to make results available, either in the form of a dissertation or publication in a peer-reviewed journal.

RESULTS:

Patient Characteristics:

A total of 149 study catheters were inserted in 149 different patients. Complete data could be evaluated for only 118 patients in the study population. The remaining 31 patients (6 with ARROW Standard CVCs, 12 with ARROWgard™ CVCs, and 13 cases in which the type of CVC was not recorded) were excluded from the analysis predominantly either because incomplete data had been collected (in 13 patient records the inserter had failed to enter the code of the CVC i.e., 5592/5593), or CVCs were removed without notification of study coordinators, or specimens were grossly contaminated during removal. Of the remaining 118 patients in whom CVCs were inserted, 62 received (uncoated) ARROW Standard CVCs and 56 received chlorhexidine/silver sulfadiazine-impregnated ARROWgard™ CVCs. If a patient received more than one catheter of either type during the course of the study period, data were collected only for the first catheterisation. Nearly all patients (113/118) were either receiving, or had recently received combinations of systemic antibiotics. With the exception of trauma cases, the two study groups were similar with regard to patient category (medical; surgical; and gynaecological). Furthermore, the two groups were comparable with regard to underlying diagnosis and risk factors (e.g., a previously inserted CVC prior to admission to ICU; mechanical ventilation; and hyperalimentation). Patient characteristics are summarised in **Table 2.**

Table 2: Patient characteristics.

Characteristic (Total number of patients (n) studied = 118)	ARROW Catheter Group *(5592)*	ARROWgard Catheter Group *(5593)*
Median age in years, (range)*	47y (17-83)	42y (18-78)
Sex **		
Total number of patients in each group: n,(%)	62	56
Male	38/62 (61%)	34/56 (61%)
Female	24/62 (39%)	22/56 (39%)
Patient category		
Total number of patients in each group: n,(%)	62	56
Medical	33/62 (53%)	38/56 (68%)
Surgical	7/62 (11%)	6/56 (11%)
Trauma	20/62 (32%)	9/56 (16%)
Gynaecological	2/62 (3.2%)	3/56 (5.3%)
Total number of patients with systemic sepsis at time of CVC insertion in each group:		
n (%)	36/62 (58%)	33/56 (59%)
Pulmonary	18/36 (50%)	18/33 (55%)
Bloodstream	7/36 (19.4%)	1/33 (3%)
Urinary tract **	- -	- -
Intra-abdominal	2/36 (5,6%)	4/33 (12%)
Gynaecological	2/36 (5,6%)	1/33 (3%)
Multiple sites	6/36 (16,7%)	7/33 (21%)
Other	1/36 (2.7%)	2/33 (6%)
Other intravascular catheter in each patient group, n (%)	6/62 (9.7%)	0/56 (0%)
Hyperalimentation (TPN) administered in each patient group, n (%)	33/62 (53%)	27/56 (48%)
Ventilation, n (%)	54/62 (87%)	55/56 (98%)

* Information recorded and available 111 of 118 patients

** Microbiologically documented involvement of the urinary tract was seen in patients with multiple site infections, (2 cases of both pulmonary and urinary tract infection in the 5592 group and 1 case of bloodstream and urinary tract infection in the 5593 group)

Table 3 below shows the median white blood cell count and temperatures of patients whose CVC was removed at the time of suspected sepsis.

Table 3: Median WCC and temperature at time of suspected sepsis.

	ARROW Catheter Group *(5592)* (n=62)	**ARROWgard Catheter Group *(5593)* (n=56)**
Median WCC X 10^9/l at sepsis, (range)	18.9 (1.8-66.6)	16.2 (5.3-31.5)
Median temperature, °C, (range)	38.1 (36.9-40.1)	38.5 (37.3-40.9)

Characteristics of central venous catheters:

All patients in whom a CVC was inserted in a clinical department, other than ICU, had their catheter removed on admission to the ICU and were randomly assigned to receive either an ARROW Standard or an ARROWgard triple-lumen CVC. Guidewire catheter exchanges were not performed in any of the patients studied. The two study groups were similar for location of catheter insertion, and reason for catheter removal. No mechanical complications of catheter insertion were observed in either group. The mean duration of catheterisation was 12 and 12.7 days for the 5592 and 5593 groups respectively (**Table 4**).

Table 4: Catheter characteristics

Characteristic:	ARROW Catheter Group *(5592)* (n=62)	ARROWgard Catheter Group *(5593)* (n=56)
Complications at catheter insertion, n (%)	0 (0%)	0 (0%)
Insertion site, n (%):		
Right internal jugular	29 (47%)	27 (48%)
Left internal jugular	23 (37%)	16 (29%)
Right subclavian	6 (10%)	11 (20%)
Left subclavian	4 (6%)	1 (3%)
Duration of placement (days):		
Mean	12	12.7
Median	14	14
Range	1-14	1-14
Duration of placement (hours):		
Mean	288.7	305.5
Median	335	335
Range	27-345	26-352
Reason for catheter removal, n (%):		
Routine removal at day 14	26/62 (42%)	24/56 (43%)
Removal at day 14 with evidence of systemic sepsis (not thought to be CVC-related)	15/62 (24%)	16/56 (28%)
Clinical suspicion of CRI (local/systemic)	15/62 (24%)	15/56 (27%)
Other, non-infective, cause [CVC no longer required, mechanical complication (e.g. occlusion), death of patient]	*6/62 (10%)*	*1/56 (2%)*

Colonisation of skin around CVC insertion site:

The mean $\log_{10}$ base counts for all bacteria cultured from 10 cm^2 of skin around the CVC insertion site prior to catheter insertion and catheter removal are shown in **Table 5.** Prior to catheter removal, sites in the four patient categories (trauma, medical, gynaecological, trauma) showed comparable levels of skin colonisation.

Table 5. Comparison of mean $\log_{10}$ base counts of bacteria cultured from skin prior to catheter insertion and pre-catheter removal.

Patient category	Mean $\log_{10}$ base count* pre-CVC insertion ARROW Standard *(5592)*	Mean $\log_{10}$ base count* pre-CVC insertion ARROWgard *(5593)*	Mean $\log_{10}$ base count* pre-CVC removal ARROW Standard *(5592)*	Mean $\log_{10}$ base count* pre-CVC removal ARROWgard *(5593)*
Trauma	3.6649	3.4929	4.0749	3.0572
Medical	3.5588	3.6758	3.0384	3.4153
Gynaecological	2.8559	5.5503	3.2041	2.7902
Surgical	4.0670	4.6521	3.8884	2.5849
TOTAL:	3.5906	3.3790	3.7905	3.6828

* **Count expressed as mean $\log_{10}$ base colony forming units (CFU)/10 cm^2 skin**

In sixty-six of the 118 patients studied, where skin swabs yielded growth both before catheter insertion and prior to catheter removal, statistical analyses showed no significant differences in the number of bacteria (expressed as $\log_{10}$ base count/10 cm^2 from the skin site prior to catheter insertion and prior to catheter removal (mean $\log_{10}$ base difference 0.483648, sd 2.244811, t = 1.75034, $p = 0.084778$). Not surprisingly, coagulase-negative staphylococci (CoNS), including some micrococci, constituted the

majority (60%) of 161 skin colonisers that were isolated. The main purpose for the recovery of these organisms was to be able to show clonality, using macro-restriction analysis, of CoNS in cases where colonisation or infection starts at the catheter insertion (exit) site and migrates along the subcutaneous tract into the bloodstream. Other bacteria isolated from skin cultures, in descending order of frequency, included Enterobacteriaceae (10%), *Bacillus* spp (7.5%), *Acinetobacter baumanii* (5%), *S aureus* (4%), enterococci (4%), diphtheroids (4%), *Pseudomonas* spp (3%) and *Streptococcus* spp (2.5%). For each of these organisms, there were no statistically significant differences ($p > 0.05$) between isolates recovered from the ARROW Standard (group 5595) and the ARROWgard (group 5593) triple-lumen CVCs.

Colonisation of CVCs:

Five of the 118 CVCs were colonised (**Table 6**) according to the definition used in this study (see Materials and Methods, page 27). Three of the 5 catheters were ARROW Standard (non-impregnated) catheters and 2 were ARROWgard (antiseptic impregnated) catheters. There were no significant differences in either the rates of colonisation or in the nature of colonising bacteria. CoNS were recovered from two of the ARROW Standard catheters and from one ARROWgard catheter. *Enterobacter cloacae* was isolated from an ARROW Standard catheter and a *Bacillus cereus* from an ARROWgard catheter. Colonised catheters were in place for a mean of 12.6 days.

Catheter-related infections:

Only 1 of 118 patients had his CVC (ARROW Standard) removed after 6 days of placement because of symptoms and signs of local CRI. There was no evidence of systemic infection in this case, and blood cultures collected both through the CVC and from a peripheral site were negative.

In 18 cases, a bloodstream infection was diagnosed. In 3 instances (1 from the ARROW Standard group and 2 from the ARROWgard group), the CVC was probably contaminated following haematogenous seeding of organisms from another site (i.e., these were not primary CVC-related infections). Of the remaining 15 cases, bloodstream infection was attributed to an indwelling study CVC. Transcutaneous infections accounted for 8 of the 15 cases [(3 CoNS, 1 *S aureus,* 1 *Serratia marcescens*) from ARROW Standard CVCs; 1 CoNS, 1 *Alcaligenes faecalis*, and 1 yeast from ARROWgard CVCs)]; hub infection for accounted for 3 cases [(1 *Klebsiella pneumoniae* from an ARROW Standard CVC; 1 *Enterobacter aerogenes,* and 1 *Acinetobacter baumanii* from each of 2 ARROWgard CVCs)]; the infusate was found to be the source in 1 case (*Providencia* spp from an ARROW Standard catheter); and in 3 cases [(2 CoNS from each of 2 ARROW Standard CVCs and multiple organisms from an ARROWgard CVC)] the source of infection could not be accurately characterised.

The mean duration of catheter placement for transcutaneous, hub and infusate-related infections was 13.6, 13.0 and 9.0 days, respectively. The mean duration of placement for all other 95 catheters (49 ARROW Standard and 46 ARROWgard) that were neither colonised nor infected was 12.4 days.

The mean duration of placement for the full sample of 118 CVCs was 12.3 days. Statistical analysis showed that there were no significant differences in the number of days of catheter placement irrespective of whether the CVCs were not colonised, colonised or were the source of infection ($p = 0.55$).

Chi-square contingency tables were used in order to determine whether the CVC insertion site and the administration of TPN had a significant impact on colonisation/infection. For all four insertion sites (viz., left subclavian, right subclavian, left internal jugular, right internal jugular), grouping colonisation and infection together failed to show a statistically significant difference ($p = 0.35$). The administration of TPN was not a significant factor ($p = 0.81$); grouping colonisation and infection together also failed to show a statistically significant difference in patients receiving TPN ($p = 0.54$).

The rates of primary catheter-related bloodstream infections (CRBs) were 12.7/1000 CVC days (9 infections for a total of 709 days for the ARROW Standard group) and days 8.1/ 1000 CVC days (6 infections for a total of 744 days for the ARROWgard™). If colonisation and all CRIs, including those secondary to haematogenous seeding, are taken together, there are no statistically significant differences irrespective of whether an ARROW Standard (14.1 CRBs/1000 CVC days) or an ARROWgard™ triple-lumen CVC (10.8 CRBs/ 1000 CVC days) is used (p value = 0.90). The results are summarised in **Table 6.**

Table 6. Summarising the data: Do ARROWgard CVCs significantly reduce CRIs when compared to ARROW Standard CVCs?

	ARROW Catheter Group *(5592)* (n=62)	ARROWgard Catheter Group *(5593)* (n=56)
No colonisation/infection	49	46
Colonised	3	2
Bloodstream infections (total) (Primary bloodstream infections, excluding haematogenous seeding of CVC)	10 (9)	8 (6)

***p* value for chi-square test of the above table (no colonisation/infection, colonised, and total bloodtream infection groups) is 0.899. If colonised and total bloodstream infection groups are combined, then *p* = 0.90445.**

The role of macro-restriction analysis in elucidating the role of CoNS in CRIs:

The usefulness of molecular epidemiological techniques in determining the etiologic role of CoNS in CRIs has been well described by Dominguez, et al (1996). Due to financial limitations, molecular typing using macro-restriction analysis was performed on only four randomly chosen study isolates (isolates 61, 85, 96, 101). See **Table 7**, and **Figures 1-4.**

Isolate 85 came from a patient with colonisation but no obvious signs of CRI, on removal of his catheter on day 14. A CoNS isolated from the skin prior to catheter removal showed genetic relatedness to a CoNS recovered from the transcutaneous

segment and what appeared to be two different morphotypes recovered from the distal segment. This patient's blood cultures were negative suggesting that the growth of the organism in the bloodstream was suppressed by prior antibiotic therapy, or that the contaminated CVC was removed in time.

Isolate 96 shows the presence of a CoNS isolated from the skin prior to the removal of the CVC, from the distal segment and from peripheral blood cultures collected from the patient, which are all genetically related. Identical CoNS with similar DNA profiles that were isolated from a segment of the colonised catheter and from the bloodstream confirmed the diagnosis of a CRB. Similarly, for isolate 61, the presence of the same clone of CoNS on the pre- catheter insertion skin swab, a catheter segment and blood cultures confirm the role of CoNS in CRB in this patient. Clearly, a mismatch cannot rule out the diagnosis of a CRB because catheter colonisation may be polyclonal within a species. This is reflected by the presence of strains showing a banding pattern with a second CoNS morphotype isolated from both the transcutaneous segment and peripheral blood cultures.

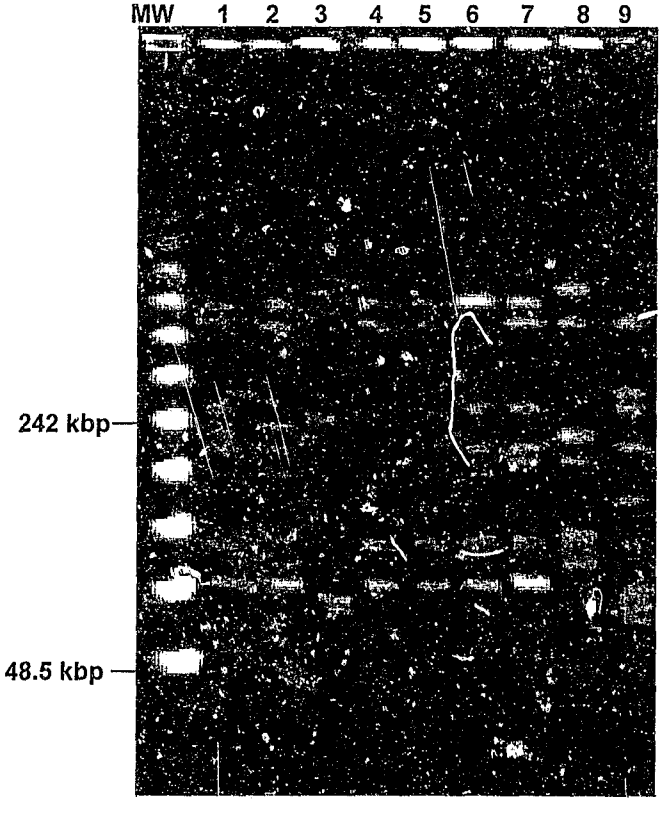

Figure 1. Macro-restriction analysis of CoNS isolates from patient 61. See Table 7 for details of lanes.

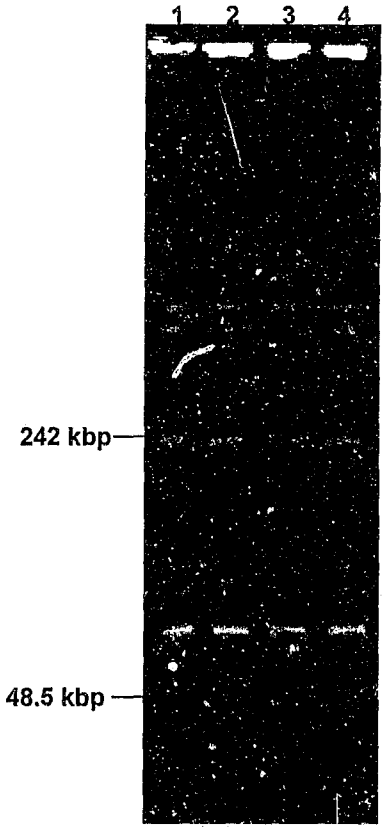

Figure 2. Macro-restriction analysis of CoNS isolates from patient 85. See Table 7 for details of lanes.

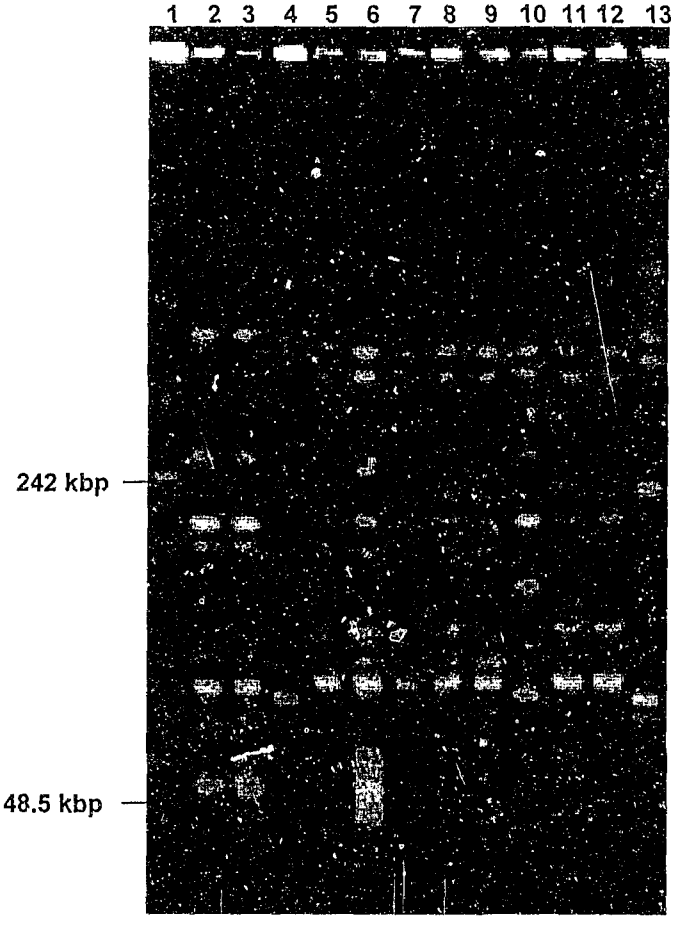

Figure 3. Macro-restriction analysis of CoNS isolates from patient 96. See Table 7 for details of lanes.

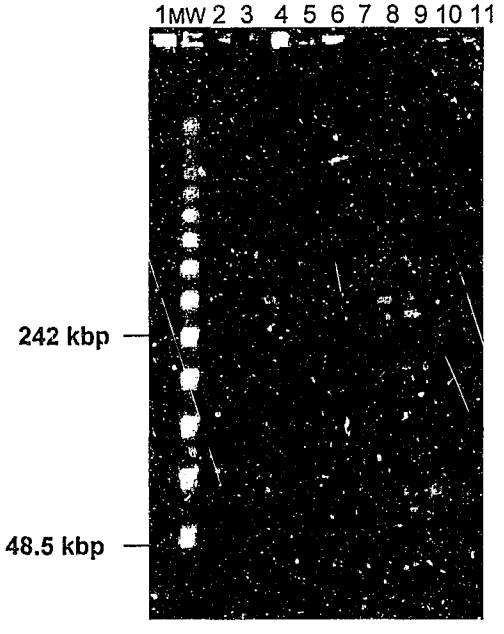

Figure 4. Macro-restriction analysis of CoNS isolates from patient 101. See Table 7 for details of lanes.

Table 7. Banding patterns assigned to coagulase negative staphylococci subjected to macro-restriction analysis.

Study number	Specimen	Figure and lane number	Banding pattern*	Relatedness**
61 (Fig. 1)	Pre-insertion skin swab	1	A	
	Pre-insertion skin swab	2	B	
	Pre-insertion skin swab	3	C	
	Pre-insertion skin swab	4	B	
	Distal segment	5	A	
	Distal segment	6	A^1	Closely related
	Distal segment	7	A^2	Closely related
	Distal segment	8	D	
	Pre-removal skin swab	9	E	
85 (Fig. 2)	Distal segment	1	A	
	Distal segment	2	A	
	Transcutaneous segment	3	A	
	Pre-removal skin swab	4	A	
96 (Fig. 3)	Pre-insertion skin swab	1	A	
	Pre-insertion skin swab	2	B	
	Pre-insertion skin swab	3	B	
	Peripheral blood culture	4	C	
	Peripheral blood culture	5	D	
	Peripheral blood culture	6	D^1	Possibly related
	Peripheral blood culture	7	D^2	Closely related
	Peripheral blood culture	8	D^2	Closely related
	Distal segment	9	D^2	Closely related
	Pre-removal skin swab	10	E	
	Pre-removal skin swab	11	D	
	Pre-removal skin swab	12	D	
	Transcutaneous segment	13	C	
101 (Fig. 4)	Pre-insertion skin swab	1	A	
	Pre-insertion skin swab	2	B	
	Pre-removal skin swab	3	B	
	Pre-removal skin swab	4	B^1	
	Pre-removal skin swab	5	B	
	Blood culture	6	A	
	Distal segment	7	B	
	Distal segment	8	C	
	Transcutaneous segment	9	C^1	Possibly related
	Transcutaneous segment	10	B	
	Transcutaneous segment	11	B	

* Banding patterns were allocated to isolates from each patient. The letters used refer to the banding patterns for each specific patient and should not be compared to patterns from other patients. Letters with numerical superscripts (e.g., $A^{1 \text{ or } 2}$) are either possibly, or closely, related to the original letter lacking the numerical superscript (i.e., A).

** PFGE patterns were interpreted using the guidelines of Tenover et al., (1995). Where similarities in banding patterns were seen, a note is made of the degree of relatedness.

Adverse Effects of CVC Catheters:

No local or systemic hypersensitivity reactions, nor any other adverse event, were noted over the duration of catheter placement or at time of removal of the catheter.

DISCUSSION:

Approximately 150 million intravascular devices are purchased each year by hospitals and clinics in the United States, placing large numbers of patients at risk for catheter-related infection (Mermel, 1996). The risk of acquiring a catheter-related bloodstream infection (BSI) varies from study to study, but ranges mainly from 0.9 to 8% (Widmer, 1997:184). These differences in reported rates probably occur because of the inclusion of different subjects in the study population (e.g., burn patients, oncology patients, intensive care patients, patients receiving TPN, etc.), the type of intravascular device used, the quality of catheter care, and duration of catheterisation. Furthermore, the nature of the intensive care unit (e.g., post-operative, trauma, general, pulmonary, coronary, etc.) also contributes to the variation in reported rates of catheter-related BSIs. Under ideal circumstances, it becomes important, therefore, to stratify data regarding catheter-related BSIs according to type of intensive care unit in which they occur.

In recent years, antibacterial substances (antiseptics or antibiotics) have been effectively bonded to catheters designed for short-term use. These catheters are referred to as "second-generation" catheters. Chlorhexidine-gluconate/silver sulfadiazine-impregnated catheters have been evaluated in several studies. A clinical investigation of 40 post-operative cardiac surgical patients showed a significantly lower incidence of microbial colonisation of catheter tips with antiseptic-bonded catheters (Bach, Geiss M, & Geiss H, 1993). Clemence et al. (1993) reported a reduction in CRBs with these catheters in a crossover study of ICU patients. There was a 60% reduction in primary bacteraemia. Maki et al. (1997) also reported the

results of a large comparative clinical study using chlorhexidine/silver sulfadiazine CVCs compared with control standard uncoated catheters. Conversely, Logghe et al. (1997) reported that chlorhexidine/silver sulfadiazine CVCs did not reduce the risk of bloodstream infection in patients with haematological malignancy. Four other clinical trials, which studied 72, 251, 282 and 308 evaluable CVCs, (Pemberton, 1996; Ciresi, 1996; Tennenberg, 1997; Heard, 1998, respectively), like the present study, showed either a nonsignificant or no trend toward lower rates of bloodstream infections when antimicrobial-impregnated study catheters were used. However, these four trials are deficient in that they are not double-blind and lack sufficient power to conclusively determine whether there are significant differences.

Inconsistencies in results as to the effectiveness of chlorhexidine/silver sulfadiazine-impregnated catheters could also be due to a variety of other factors. These include: categories of patients studied; differences in skin preparation protocols; average duration of catheterisation; quality of CVC care during insertion and maintenance; and the sensitivity of the culture techniques used for the microbiological diagnosis of CVC-related colonisation or infection.

Darouiche et al. (1999), conducted a study comparing colonisation and CRB rates in patients receiving either minocycline/rifampicin- or chlohexidine/silver sulfadiazine-impregnated catheters. The investigators reported reduced rates of CRB (0.3% versus 3.4%) in each of the two groups respectively. Catheter colonisation occurred in 7.9% of catheters impregnated with minocycline/rifampicin versus 22.8% of the catheters impregnated with chlorhexidine/silver -sulfadiazine. Both colonisation and CRB rates

were, in their study, higher for chlorhexidine/silver sulfadiazine catheters than those reported by Maki et al. (1997), which were 13.5% and 1% respectively.

The main objectives of this study were: 1) to elucidate the epidemiology of CVC-related infections in the General Intensive Care Unit of the Johannesburg Hospital; 2) to determine whether the use of chlorhexidine/silver sulfadiazine-impregnated (ARROWgard ™) CVCs can significantly decrease the incidence of catheter-related infections (resulting in overall cost savings) versus the use of ARROW Standard CVC at 14 days; and 3) to determine whether the duration of catheter insertion can be safely increased to 14 days.

At the outset, several important limitations of this study need to be considered. Firstly, as mentioned previously in this report (see section on Study design and Population, Materials and Methods, pp 33-34) due to budgetary constraints and unexpected termination of funding we were unable to get the required minimum sample size of 176 patients to reach a statistically significant conclusion (assuming a confidence interval of 95%, power of 80%, equal numbers of patients in each group, and a relative risk of 4). Secondly, 31 of the 149 patients in whom study catheters were inserted were excluded from the study because critically important data, such as whether the catheter was coded 5592 (uncoated) or 5593 (coated) were omitted from patient records. Consequently, because it was not possible to determine how many of the excluded catheters were impregnated with chlorhexidine and silver-sulfadiazine, a bias could have been introduced in the results. Thirdly, although it is a problem commonly encountered, yet infrequently acknowledged in most studies investigating CVC-related sepsis, the vast majority of our catheterised patients had been on courses

of broad-spectrum, systemic antibiotics, that might have impaired the adequate recovery of microorganisms. Fourthly, again primarily because of economic constraints, we decided to perform only the Maki semi-quantitative roll-plate method and to correlate it with clinical results rather than to additionally conduct quantitative cultures following sonication of the transcutaneous and distal segments of the CVC. This latter approach would have enabled retrieval of organisms from both the external and internal surfaces of the catheter. Yet, there was rationale (other than financial) for not including quantitative cultures. Firstly, the antimicrobial activity of catheters impregnated with chlorhexidine and silver sulfadiazine is limited to the external surface; hence, to estimate the impact of antimicrobial surface coating, the roll-plate technique would, for the purposes of this study, suffice. The limited sensitivity of the Maki roll-plate technique used alone for the diagnosis of catheter colonisation and CRB, is described in other reports (Sherertz, 1990; Sherertz et al., 1997). Despite this, however, catheters impregnated with chlorhexidine and silver sulfadiazine have been shown to reduce colonisation of the external surface as compared with uncoated catheters in studies in which the roll-plate method alone was used to culture the catheter tips, or both the catheter tips and the transcutaneous segments. Some of the other antibiotic- (e.g., minocycline and rifampicin) impregnated CVCs that have antimicrobial activity on both the extra- and intraluminal surfaces of the catheter would have necessitated a different approach to culture. Secondly, the results of this study should be interpreted within the framework of methods and data analysis. All our catheters were triple-lumen polyurethane catheters placed through a new percutaneous insertion site (not exchanged over a guidewire) for a relatively short period (1-14 days). The findings by Raad et al. (1993), that external colonisation is predominant in the 10 first days of catheter placement while intraluminal colonisation

becomes predominant after 30 days, would indicate that the semi-quantitative roll-plate technique would be most useful for short-term catheters (as were most of the catheters in the original study by Maki et al. (1977), whereas for long-term catheters the internal surface should be cultured.

To the best of my knowledge, this is the first study conducted in South Africa documenting the epidemiology and rates of CVC-related infections (expressed per 1000 days) in ICU patients, using the synthesis of both clinical and microbiological definitions as proposed by the CDC. The General ICU of the Johannesburg Hospital is a multidisciplinary unit that admits critically ill trauma, medical, gynaecology and surgical patients.

Data presented in this report on the types of colonising organisms (predominantly skin colonisers) and those causing infections via the transcutaneous route are consistent with those described in other studies. The routes of catheter infection in our patients, viz., mainly transcutaneous and the catheter hub, are likewise well documented in the literature (Widmer, 1997; Maki & Mermel, 1998).

There was no statistically significant difference in total bloodstream infection rates between the group of patients who received ARROW Standard catheters (14.1 CRBs/1000 CVC days) and those who received ARROWgard catheters (10.8 CRBs/ 1000 CVC days). If only primary bloodstream infections are considered (i.e., excluding haematogenous seeding of the CVC) there is still no statistically significant difference in CRI rates between the 2 catheter groups (12.7 CRIs/1000 CVC days and 8.1 CRIs/1000 CVC days for the ARROW Standard and ARROWgard ™ CVCs

respectively). It is pertinent to note that the absence of statistical significance between the 2 groups was noted despite the fact that the ARROW Standard CVC group included more than double the number of trauma patients than the ARROWgard ™ group (20/62 [69%] versus 9/56 [31%] respectively). Furthermore, all patients with an additional intravascular catheter other than a CVC (6/118 [5.1%]) all belonged to the ARROW Standard group. Trauma patients as well as patients with other intravascular devices are, for obvious reasons, more likely to be susceptible to CRIs. Statistical analyses showed, in this study, that it was significant that more than double the number of trauma patients (p = 0.04) and all patients with other intravascular devices (p = 0.016) belonged to the ARROW Standard group with no apparent difference in infection rates in the 2 groups.

The overall incidence of CRIs in the medical literature is variable, ranging from 4%-18% (Elliott & Tebbs, 1998). The incidence of infection markedly varies with patient groups and their underlying condition. For instance, patients in respiratory ICUs have a reported infection rate of 2.1/1000 CVC days whereas in a burn unit this can rise to over 30/1000 CVC days. Acknowledging the fact that the ICU in which our study was conducted was of a multidisciplinary nature, it is possible that our recorded infection rates, though they seem somewhat high, are reasonable given the varied case-mix in our ICU. Other possible explanations for this high rate of infections include inadequate infection control practices and the fact that catheters were left *in situ* for up to 14 days. In view of the fact that it is difficult to make a clinical diagnosis and/or laboratory diagnosis of a CRI, with patients frequently showing no symptoms/signs of infection at the catheter insertion site, I hesitate to conclude that CVCs can be safely left in place for as long as 14 days. Daily inspection of the catheter insertion site

would not, as discussed previously in this report, necessarily have resulted in early detection of CRIs. Further studies carried out in multi-disciplinary intensive care units will be required to determine an acceptable range of infection rates in this setting. Such studies should also investigate the optimal duration of CVC placement. Until such time that this information becomes available, it seems prudent to remember two golden rules in CVC management. Firstly, novel CVCs with antibacterial properties are not a substitute for, but rather an adjunct to, intelligent and rigorous infection control practice. Secondly, no CVC should be left in place longer than is necessary.

In the United States it has been estimated that the direct (attributable) mortality from nosocomial bloodstream infections (BSIs) is 25% (Wenzel & Edmond, 1999). Thus, the annual burden of hospital-acquired BSIs is 25% of at least 200 000 nosocomial BSIs, or 50 000 deaths. Recent data show that 70% of all nosocomial bloodstream infections occur in patients with CVCs (Jones, Marshall & Pfaller et al., 1997). Even if less than 50% of these infections are directly related to CVCs, it is obvious that minimising CRIs (including the use of antimicrobial-bonded CVCs) could incur a substantial saving by reducing morbidity and mortality of seriously ill patients.

Pittet et al (1994) and Heiselman (1994) estimated that the extra cost of treating one episode of catheter-related infection in a critically ill patient was US $28 690 (SAR 172 794) per survivor. Fifty-percent of these episodes were caused by CoNS and each episode resulted in an additional stay in the intensive care unit of 6.5 days. If, again, we take a conservative estimate of cost-benefit by assuming that the cost of a CRB is half that of Pittet et al and Heiselman (US $14 345) then this would translate into

SAR 86 397. Clearly, such figures cannot be extrapolated to deduce the cost of a CRB in the South African health care setting but it suffices to say that these infections are exorbitantly expensive to treat. Regrettably, accurate data of the economic consequences (direct and indirect) of nosocomial infections in South Africa are lacking. In a study of 405 CVCs by Maki et al. (1997), ARROWgard™ CVCs were 2-fold less likely to be colonised than non-antiseptic-impregnated catheters (ARROW Standard) and 4-fold less likely to produce CRB. Based on their results, the purchase of these devices could potentially result in large overall savings, although this study has been criticised for several reasons. Firstly, this study looked predominantly at short-term catheters (*in situ* for < 8 days). Secondly, the study was not double-blind. Thirdly, only the Maki roll-plate technique was used (i.e., no intraluminal cultures after sonication of catheter segments were performed). Consequently, cases of CVC intraluminal colonisation could have been missed. Fourthly, other studies such as that of Darouiche et al. (1999), failed to show the same dramatic decreases in both CVC colonisation and infection .

In contrast, the present research report, and four other literature studies (Pemberton, 1996; Ciresi, 1996; Tennenberg, 1997; Heard, 1998, respectively), have shown that chlorhexidine/silver sulfadiazine-impregnated catheters are only slightly, if at all, better than first-generation catheters which are not coated with antibacterial substances. The current cost of an ARROW Standard triple-lumen catheter is SAR 264.88 whereas that of an ARROWgard catheter is SAR 364.50.

In view of the fact that currently available data are inadequate to permit a firm judgement on the anti-infective benefits of chlorhexidine/silver sulfadiazine-

impregnated catheters, I would not encourage hospitals to spend substantial sums of money on ARROWgard CVCs until the ongoing debate of whether these catheters significantly reduce infections, and are therefore cost-effective, is finally resolved. For this to occur, more concrete data from double-blind, randomised, studies enrolling larger numbers of patients to receive either standard or antiseptic-impregnated CVCs must become available. Until such data becomes available, meticulous infection control practice prior to and during catheter insertion and removal should be the primary strategy in reducing the costs incurred from CRIs.

APPENDIX A: PROTOCOLS FOR SPECIMEN COLLECTION

PROTOCOL A: to be carried out on all patients enrolled in the trial.

Culture of skin insertion site prior to CVC insertion:

a) Culture of skin insertion site must be performed prior to preparing the CVC skin insertion site and draping the patient.

b) After washing hands, and wearing sterile gloves, place a sterile template over intended CVC insertion site.

c) Pre-moisten the applicator stick (swab) by dipping it several times in Stuart's transport medium.

d) Rotating the pre-moistened swab, vigorously scrub the entire area delineated by the inner border of the template (made using an X-ray plate, sterilised by ethylene oxide between uses) (total area 10 cm^2) four times, twice in one direction, and then twice more in a direction perpendicular to the first.

PROTOCOL B: to be followed if line is removed after 14 days with no evidence of local/systemic sepsis.

a) Prior to the removal of the CVC, swab 10 cm^2 of skin about the catheter site.

b) Collect one aerobic, one anaerobic Bactec® bottle and 1 fungal culture aseptically through the CVC.

c) Collection of catheter segments for culture:

- To prevent contamination by skin microorganisms, the skin insertion site will be cleaned with 0.5% chlorhexidine in 70% alcohol after a quantitative culture skin swab has been collected from the insertion site.

- The catheter must be removed keeping the externalised portion directed upward and away from the skin surface to minimise contamination by skin organisms.

- Two portions of the catheters must be submitted for microbiological processing: the transcutaneous segment and the distant intravascular tip. These segments of the catheter will be cut with a sterile scalpel and will be 5 cm long. The two segments must be individually (separately) placed in appropriately labelled, sterile universal containers and submitted to the laboratory for culture within 2 hours of collection to prevent desiccation of microorganisms.

PROTOCOL C: to be followed if there is any evidence of local/systemic sepsis.

a) Prior to CVC removal, swab the skin insertion site as described in protocol B.

b) Aseptically collect 10 ml of each administered infusate at the time of CVC removal into an appropriately labelled, sterile universal container.

c) Using sterile cotton-tipped applicators (swabs), which have been pre-moistened in Stuart's transport medium, each catheter must be swabbed (total of 3 swabs) by aseptically inserting the cotton tipped applicator into the hub and, while exerting gentle axial pressure, rotating the applicator. Each swab must be placed into a suitably labelled container (i.e., from blue, brown, or yellow hubs).

d) Blood cultures must be collected as follows:

- 2 aerobic Bactec® bottles (5 ml of blood in each bottle), 2 anaerobic Bactec® bottles (5 ml of blood in each bottle) and 1 fungal blood culture must be collected aseptically through the CVC.

- 2 aerobic Bactec® bottles (5 ml of blood in each bottle), 2 anaerobic Bactec® bottles (5 ml of blood in each bottle) and 1 fungal blood culture must be collected aseptically from a peripheral site.

e) Collection of catheter segments for culture: as described in Protocol B.

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