# CENTRAL VENOUS CATHETER-RELATED INFECTION

A thesis submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor of Philosophy

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## DECLARATION

I, Mervyn Mer declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

..... .....

Signature Date

## DEDICATION

This thesis is dedicated to my parents, Morris and

Lily - special people - and to my family, Avril, Myron,

Brett and Jonty for their unconditional love, support and patience

## PRESENTATIONS, PUBLICATIONS AND AWARDS ARISING FROM THIS STUDY

### Presentations:

Multiple presentations at Critical Care Society of Southern Africa National Congresses and Refresher Courses, Pulmonology Congresses, Anaesthesiology Congresses and Refresher Courses, and the Southern African Society of Thrombosis and Haemostasis Congress. These have included presentations of the original study data, as well as plenary sessions on the subject.

Several presentations at regional and local meetings and symposia.

22nd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium ("Central Venous Catheter-Related Infection").

### Publications:

Mer M. Intravascular catheter related infection. S Afr J Crit Care 1999;15(2):30-35.

Mer M. Vascular catheter related infection. Clinical Intensive Care 2001;12(2):53-60.

Mer M, Duse AG, Galpin J, Taylor R, Richards GA. Central venous catheter-related infection. Abst. Critical Care 2002;6(S1):S94.

Mer M. Nosocomial bloodstream infection. South Afr J Epidemiol Infect 2005; 20(2):61-62.

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Brink A, Feldman C, Duse A, Gopalan D, Grolman D, Mer M, Naicker S, Paget G, Perovic O, Richards G. Guideline for the Management of Nosocomial Infections in South Africa. S Afr Med J 2006;96(2):641-652.

Mer M. Intravascular catheter-related infection: current concepts. S Afr J Crit Care 2006; 22(1):4-12.

Mer M. Nesibopho guideline on Intravascular Catheter-related Infection – Critical Care Society of Southern Africa endorsed and independently peer-reviewed 2007.

Mer M. Intravascular catheter-related infection: update and overview. CME 2008; 26(11):540-544.

Mer M, Duse AG, Galpin J, Richards GA. Central venous catheterization. A randomized prospective study. Clin Appl Thromb Hemost 2009;15(1):19-26. (published early on line)

**Awards**

Best presentation by a Doctor at Critical Care Society of Southern Africa Congress held at Sun City 2001

Best paper in a peer reviewed journal awarded by the Critical Care Society of Southern Africa 2009 – “Central venous catheterization: A prospective randomized, double-blind study” published in Clinical and Applied Thrombosis / Hemostasis February 2009

**ABSTRACT**

**Introduction and Background:** Central venous catheters (CVCs) are extensively used worldwide. Mechanical, infectious and thrombotic complications are well described with their use and may be associated with prolonged hospitalisation, increased medical costs and mortality.

CVCs account for an estimated 90% of all catheter-related bloodstream infections (CRBSI) and a host of risk factors for CVC-related infections have been documented. These include, most importantly, the duration of catheterisation. The duration of use of CVCs remains controversial and the length of time such devices can safely be left in place has not been fully and objectively addressed in the critically ill patient. Over the past few years, antimicrobial impregnated catheters have been introduced in an attempt to limit catheter-related infection (CRI) and increase the time that CVCs can safely be left in situ. Recent meta-analyses concluded that antimicrobial-impregnated CVCs appear to be effective in reducing CRI.

**Materials and Methods:** This was a prospective randomised double-blind study performed in the adult multidisciplinary Intensive Care Unit (ICU) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a four year period. The study entailed a comparison of standard triple-lumen versus antimicrobial impregnated CVCs on the rate of CRI. The aim was to determine whether the duration of catheter insertion time could safely be increased from the standard practice of seven days at the CMJAH adult multidisciplinary ICU to 14 days, to assess the influence of the antimicrobial impregnated catheter on the incidence of CRI, and to elucidate the epidemiology and risks of CRI.

**Results:** One hundred and eighteen critically ill patients were included in the study which spanned 34 951.5 catheter hours (3.99 catheter years). Sixty-two patients received a standard triple-lumen catheter and 56, a chlorhexidine-silver sulfadiazine (CSS) impregnated triple-lumen catheter. The mean duration of placement for the full sample of

118 CVCs was 12.3 days (range, 1-14). No statistically significant difference in CRI rates between the two types of catheters could be demonstrated. The most common source of primary CRBSI was skin, followed by hub and infusate. The site of CVC insertion (internal jugular versus subclavian vein) and the use of parenteral nutrition were not noted to be risk factors for catheter infection. There was no clinical evidence of catheter-related thrombosis in either of the study groups.

**Conclusion:** This study was unable to demonstrate that antimicrobial catheters provided any significant benefit over standard catheters, which it is felt, can safely be left in place for up to 14 days with appropriate infection control measures. The most common source of CRI was the skin. The administration of parenteral nutrition and the site of catheter insertion (internal jugular vein versus subclavian vein) were not noted to be risk factors for CRI. There was no clinical evidence of thrombotic complications in either of the study groups. This study offers direction for the use of CVCs in critically ill patients and addresses many of the controversies that exist.

Key Words: central venous catheters, infection, duration, thrombosis

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| | |
|---|---|
| AAP: | Accumulation-associated protein |
| AOLC: | Acridine orange leucocyte cytospin |
| AtiE: | Autolycin |
| BSI: | Bloodstream infection |
| CAPD: | Central Auditory Processing Disorder |
| CFU: | Colony forming unit |
| CI: | Confidence interval |
| Clf: | Clumping factor |
| CMJAH: | Charlotte Maxeke Johannesburg Academic Hospital |
| CoNS: | Coagulase-negative *Staphylococcus* |
| Cps: | Capsular polysaccharides |
| CRBSI: | Catheter-related bloodstream infection |
| CRI: | Catheter-related infection |
| CSS: | Chlorhexidine silver sufadiazine |
| CVC: | Central venous catheter |
| EDTA: | Edetic acid |
| ELISA: | Enzyme linked immunosorbent assay |
| EPIC: | European Prevalence of Infection in Intensive Care |
| HICPAC: | Healthcare Infection Control Practices Advisory Committee |
| HR: | Hazard ratio |
| *ica:* | Intercellular adhesion |
| ICU: | Intensive care unit |
| IDSA: | Infectious Diseases Society of America |
| IgG: | Immunoglobulin G |
| INICC: | International Nosocomial Infection Consortium |
| JK: | Jeikeium |

| | |
|---|---|
| MBC: | Minimum bacterial concentration |
| MIC: | Minimum inhibitory concentration |
| MR: | Minocycline-rifampin |
| MRSA: | Methicillin-resistant *Staphylococcus aureus* |
| MSSA: | Methicillin-susceptible *Syaphylococcus aureus* |
| NEMIS: | National Epidemiology of Mycosis Survey |
| NNIS: | National Nosocomial Infection Surveillance |
| OR: | Odds ratio |
| PIA: | Polysaccharide intercellular adhesion |
| PIA: | Polysaccharide Intercellular Adhesion |
| PICC: | Peripherally inserted central venous catheter |
| PMMA: | Polymethylmethacrylate |
| PNB: | Polymixin-neomycin-bacitracin |
| PVC: | Polyvinyl chloride |
| RKI: | Robert Koch Institute |
| RR: | Relative risk |
| S aureus: | *Staphylococcal aureus* |
| SCOPE: | Surveillance and Control of Pathogens of Epidemiological Importance |
| SICU: | Surgical intensive care unit |
| SPC: | Silver platinum/carbon |
| ™: | Trademark |
| UK: | United Kingdom |
| US: | United States |
| USA: | United States of America |
| vs: | versus |

## CHAPTER 1

## INTRODUCTION

Intravascular devices are an integral component of modern-day medical practice, particularly in intensive care units [1]. They are used to administer intravenous fluids, medications, blood products and parenteral nutrition. In addition, they serve as a useful monitor of the haemodynamic status of critically ill patients [2,3,4,5].

Infection is one of the leading complications of intravascular catheters and is associated with increased mortality, prolonged hospitalisation and increased medical costs [6-19]. Central venous catheters (CVCs) account for the vast majority of all catheter-related bloodstream infections (CRBSI) [2,3,5,20-24].

Several risk factors have been documented for CVC-related infections which include very importantly, the duration of catheterisation [25-30], location of the catheter (internal jugular vein greater than subclavian vein), the use of parenteral nutrition, multilumen catheters (increased manipulation), experience of personnel inserting the device, less stringent barrier precautions during placement, type of dressing, the presence of sepsis, catheter care after placement, and the presence of CVC-related thrombi [29-32].

The duration of use of CVCs remains controversial and the length of time they can safely be left in place has not been fully and objectively addressed in the critically ill patient [33,34].

Over the past few years antimicrobial impregnated catheters have been introduced in an attempt to limit catheter-related infection (CRI) and increase the time that CVCs can safely be left in situ. A recent meta-analysis concluded that chlorhexidine silver sulfadiazine (CSS) CVCs appear to be effective in reducing CRI [35] and two other meta-analyses have reached similar conclusions [36,37].

The topic remains extremely controversial with differing viewpoints appearing in the literature in recent years [38,39,40].

## CHAPTER 2

## BACKGROUND AND HISTORY

Just over a century ago, no means of vascular access existed for the life-sustaining support of critically ill patients. In the late 1800s steel needles became available, and with the advancing knowledge of electrolyte physiology, the therapeutic use of intravenous fluid became established [2,3,4,5,41]. In 1945, following the advent of penicillin and the need for multiple intravenous injections, plastic catheters for 'continuous' vascular access were described [42,43]. Further technological advance took place in 1967 when the placement of long nylon catheters into central veins to limit medication-associated phlebitis was described in oncology patients [44]. These catheters were initially inserted by peripheral cut-down techniques and later via percutaneous approaches into the subclavian and jugular veins. Over the past two decades the focus of research and development has been on the physicochemical properties of catheters, looking at such aspects as improved catheter materials, tensile strength, rupture resistance, biocompatibility and the creation of catheter micro-environments hostile to invading organisms. Research on polymers has lead to the development of materials such as silicone, polyvinyl chloride, Teflon and polyurethane [45,46].

The advent and evolution of intravascular devices have represented a major advance in terms of patient comfort and care, but with them has come the burden of complications including a variety of local and systemic infectious complications. This includes local site infection, CRBSI, septic thrombophlebitis, endocarditis and other metastatic infections, e.g. lung abscess, brain abscess, osteomyelitis and endophthalmitis. In general, intravascular devices can be divided into those used for short-term (temporary) vascular access and those used for long-term (indwelling) vascular access. Examples of long-term devices include those described by Hickman, Broviac and others [47,48]. Long-term intravascular devices usually

require surgical insertion while short-term devices can be inserted percutaneously. The main focus in this review relates to short-term catheters.

## CHAPTER 3

## MAGNITUDE OF THE PROBLEM AND EPIDEMIOLOGY

### 3.1 Nosocomial Infections

Nosocomial infections are a leading cause of morbidity and mortality among hospitalised patients. These infections now involve 5% to 15% of hospitalised patients and can lead to complications in 25% to 50% of those admitted to intensive care units (ICUs) [49,50].

Preventable adverse events in the United States of America (USA), including nosocomial infections, are responsible for 44,000 to 98,000 deaths annually and represent a cost of $17 to $29 billion [51]. Comparable data published in the United Kingdom (UK) [52] suggests that at least 100,000 infections are acquired in hospitals in England each year. These infections may be responsible for at least 5000 deaths annually, with cost estimates as high as £1.2 billion [53].

It has been repeatedly shown that intravascular devices are among the most significant risk factors for the development of nosocomial infection [50,54-57].

### 3.2 Intravascular catheters, central venous catheters and catheter-related infections

Specific statistics are unavailable in many countries, but currently clinics and hospitals in the USA purchase more than 150 million intravascular devices annually [3,58]. This includes more than five million central venous catheters. In the USA, 15 million CVC days occur in intensive care units each year [1,59]. Globally, CRI remains among the top three causes of hospital-acquired infections [2,3,4,5].

Intravascular catheters are the leading source of bloodstream infection in critically ill patients [60.] Data regularly reported by the National Nosocomial Infection Surveillance (NNIS) system, evaluating only ICUs, indicates that most nosocomial bloodstream infections are associated with the use of intravascular access, with rates substantially higher among patients with

central venous catheters than among those with peripheral lines [61,62]. More than 85% of primary bacteraemia are considered catheter-associated [50,63-68].

Bloodstream infections represented 12% of all nosocomial infections reported in 10,038 patients from 1417 ICUs in the European Prevalence of Infection in Intensive Care (EPIC) Study [54].

Central venous catheters account for an estimated 90% of all CRBSI [2,3,4,5,20-24]. These devices are inserted in at least half of intensive care unit patients [60]. In multidisciplinary ICUs in Germany, 82% of patients were noted to have had central venous catheters placed [69].

It is estimated that at least 80 000 CVC-related bloodstream infections occur in ICUs in the USA each year [15,59,60,70], with the number increasing to 400,000 if entire hospitals are assessed rather than ICUs exclusively [1,71-73].

In addition to being a common cause of hospital-acquired infection, catheter-related bloodstream infections are potentially lethal with a mortality of up to 35%, result in prolonged hospitalisation (on average > 1 week), as well as increased medical costs [1-12,15,19,59,60,73-75] (see Table 1). It has been suggested that in the USA alone, treating such infections each year could cost up to $2.3 billion, with an average cost of care per patient of $45,000 [1,15,71,76].

Therefore, by several analyses the cost of CVC-associated BSI is substantial, both in terms of morbidity and in terms of financial resources expended.

Reported rates of CRBSI vary, with ranges from 1 to 60 per 1000 central catheter days. In general, lower rates are reported from established units in developed countries as compared to facilities in developing countries [2,3,4,5,17,59,60,70,77-79].

### 3.3 Relevance

Given the magnitude and seriousness of the problem of CRI, it has been advocated that all healthcare workers involved with their use have a clear understanding of the subject and of new developments in the field [5], as most of these infections can be reversed with appropriate diagnosis and treatment and, most importantly, many can be prevented [5,77].

### 3.4 Developing countries

The use of CVCs and CRBSI is of particular relevance to practice in South Africa and its geographic region, based on the findings of the recently completed and published International Nosocomial Infection Consortium (INICC) study, as well as a review on central-line associated bloodstream infections in resource-limited countries [5,17,77].

The INICC study evaluated device-associated infections in 55 intensive care units in eight developing countries and compared the results with pooled data from the USA. There was a significant increase in the number of central venous catheter-associated bloodstream infections in so-called developing countries as compared with units in the USA (approximately a 4-fold increase) [5,80].

A review of the literature in resource-limited countries revealed central venous origin CRBSI rates of up to 44.6 cases per 1,000 central line days in adult intensive care units and up to 60 cases per 1,000 central line days in neonatal ICUs [77] (see Table 2). These infections were associated with significant extra mortality [77,80], the odds ratio ranging from 2.8 to 9.5. Interestingly, these rates allude to hospitals in which some form of organisational health care structure exists [77,80] (see Table 3).

Countries evaluated in this review included Argentina, Brazil, Colombia, India, Iran, Mexico, Peru, Thailand, Tunisia and Turkey.

Low-income and middle-income economies, often referred to as developing countries, low-resource countries, or emerging countries, represent 145 (69.0%) of 210 countries of the world and more than 75% of the world population.

The World Bank classifies countries into four economic strata according to 2007 gross national income per capita per year. These groups are as follows: low income, US$ 935 or less; lower middle income US$ 936 - US$ 3705; upper middle income US$ 3606 - US$ 11455 and high income US$ 11456 or more [77,81].

Guidelines for the management and prevention of nosocomial infections in South Africa, including intravascular infections, have recently been published [20,82,83] and are in the process of being updated.

**Table 1**
**Impact of Catheter-Related Bloodstream Infections in Critically Ill Patients**

| | Mortality | | Attributable | |
|---|---|---|---|---|
| **Author & Reference** | **Crude** | **Attributable** | **Los [a] (day)** | **Costs (US$)** |
| Pittet [84] | 45% | 25% | 6.5 | 29,000 |
| Soufir [73] | 50% | 29% | - | - |
| Rello [13] | 22% | 13% [b] | 20.0 | 4,000 |
| Renaud & Brun-Buisson [85] | 39% | 12% [b] | 14.0 | - |
| Dimick [76] | 56% | 35% | 20.0 | 71 443 [c] |
| Warren [19] | 51% | - | 2.41 | 11,971 |

[a] Los: length of stay
[b] Differences are non-significant
[c] Based on billing database

**TABLE 2**
**Central Venous Catheter-related Bloodstream Infection Rates in ICUs in Developing Countries**

| Country & reference | Year | Type of ICU | CRBSI rate (95% CI) |
|---|---|---|---|
| Argentina [86] | 2003 | Medical-Surgical | 44.6 (32.2 - 60.0). |
| Argentina [87] | 2004 | Medical-Surgical | 30.3 (25.4 - 35.7) |
| Brazil [88] | 2003 | Burns | 34.0 (21.8 - 35.5) |
| Brazil [89] | 2002 | Neonatal | 60.0 (36.5 - 92.3) |
| Brazil [90] | 2003 | Paediatric | 10.2 - 7.2 - 16.7) |
| Argentina [87] | 2004 | Coronary | 14.2 (9.0 - 21.2) |
| Iran [91] | 2003 | Burns | 17.0 (11.6 - 24.5) |
| Mexico [92] | 2006 | Medical-Surgical- Neurosurgical | 23.1 (19.5 - 22.1) |
| Tunisia [93] | 2007 | Neonatal | 14.8 (9.2 - 20.5) |
| Turkey [94] | 2009 | Medical-Surgical | 17.6 (15.8 - 19.3) |
| India [95] | 2011 | Tertiary Care Hospital | 8.75 |

**Adapted from Rosenthal 2009 [77]**

**TABLE 3**

**Central line-associated bloodstream infection: extra mortality in developing countries**

| Country | Year | ICU population | Mortality % | | OR (95% CI) |
|---|---|---|---|---|---|
| | | | CRBSI | Non-DAI | |
| Argentina | 2003 | Adult medical-surgical | 62.5 | 37.2 | 2.3 (1.0-7.8) |
| Argentina | 2003 | Adult medical-surgical-coronary | 54.2 | 29.6 | 2.8 (1.7-4.5) |
| Mexico | 2007 | Adult medical-surgical-neurosurgical | 41.8 | 21.8 | 2.5 (1.1-5.9) |
| Thailand | 2004 | Neonatal | 27.0 | 7.0 | 5.2 (2.1-12.5) |
| Tunisia | 2007 | Neonatal | 42.0 | 5.7 | 9.5 (4.6-19.7) |

CI = Confidence interval
DAI = Device-associated infection
ICU = Intensive care unit
OR = Odds ratio

**Adapted from Rosenthal 2009 [77]**

## CHAPTER 4

## DEFINITIONS

Definitions relating to intravascular catheter infection have been put forward by various workers, but many have complicated matters and been confusing [2,3,4,5]. In part, this has been because definitions used for surveillance and research purposes have differed from those used for clinical diagnosis. The Centers for Disease Control and Prevention have suggested sensible definitions [1,4,96] that incorporate both clinical and laboratory evidence of catheter infection. These should be universally used in the definitions of intravascular catheter infection and are documented in modified form in Table 4 [2,3,4,5].

**Table 4 Definitions for catheter-related infections**

| Item | Definition |
|---|---|
| Catheter colonisation | Growth of ≥15 colony-forming units (semiquantitative culture) or ≥103 colony-forming units (quantitative culture) from a proximal or distal catheter segment in the absence of local or systemic infection. |
| Local infection | Erythema, tenderness, induration or purulence within 2cm of the skin insertion site of the catheter. |
| Infusate-related BSI | Concordant growth of the same organism from the infusate and blood cultures (preferably percutaneously drawn) with no other identifiable source of infection. |
| Catheter-related bloodstream infection | Isolation of the same organism (i.e. the identical species as per antibiogram from cultures, semiquantitative or quantitative) of a catheter segment and from the blood of a patient with accompanying clinical symptoms and signs of bloodstream infection and no other apparent source of infection. |

## CHAPTER 5

## PATHOGENESIS OF CATHETER-RELATED INFECTIONS

### 5.1 Overview of the pathogenesis (see Figure 1)

The skin around the insertion site is the most common portal of entry [4,60,97-99]. Following placement, a fibrin sheath develops around the catheter which promotes the adherence of pathogens and is known as the biofilm layer. Skin organisms then migrate from the insertion site along the external surface of the catheter to colonise the distal intrasvascular tip and ultimately cause bloodstream infection [69,97,100,101].

Contamination of the catheter during the manipulation by medical and nursing personnel is the second most common portal of entry of micro-organisms [4,98,102-108].

Less common causes include haematogenous dissemination from a distal infectious focus, administration of contaminated infusates, and contaminated transducer kits, disinfectants and infusion lines [107-110].

### 5.2 Biofilm

The importance of biofilm formation in vascular catheter infections is becoming increasingly apparent. Microbial colonisation and biofilm formation occurs shortly after the catheter insertion [111] which may subsequently cause bacteraemia. The composition of biofilm, includes various blood and tissue proteins, fibrin, fibronectin, fibrinogen, collagen, elastin, thrombospondin, laminin, vitronectin and von Willebrand's factor, in combination with exopolysaccharide material produced by colonising pathogens (slime, glycocalyx) [112-120]. The complex matrix or biofilm protects the bacteria or other pathogens from chemotherapeutic agents and opsonophagocytosis [121].

The greatest progress in understanding the importance of biofilms in the pathogenesis of catheter-related infection has occurred with *Staphylococcus epidermidis (S.epidermidis)*. Initial attachment appears to be mediated by a protein autolysin (AtlE) [122,123]. Subsequent adherence and biofilm formation are mediated by polysaccharide intercellular adhesion (PIA) [124-126]. In a rat model, *S. epidermidis* isolates that lack AtlE or PIA are significantly less likely ($p<0.05$) to cause catheter infection, peripheral bacteraemia and metastatic infection [127,128]. The intercellular adhesion (*ica)* operan that encodes for PIA in *S. epidermidis* can also be found in *Staphylococcus aureus* (*S. aureus)* isolates from patients with catheter-related infection or prosthetic joint infection [129,130].

The *ica* locus appears to be regulated by the *agr* quorum-sensing system [131], *S. aureus* strains that are *agr*-positive are unlikely to form biofilms (6%), whereas *agr*-negative strains form biofilms 78% of the time. Blockers that can inhibit *S. aureus* quorum sensing increase biofilm formation. As quorum sensing blockers are being considered as adjuncts to antibiotic therapy, biofilm formation may actually be augmented in this setting. This could paradoxically decrease the efficacy of antibiotics by increasing the amount of any drug necessary to kill the organism 100-1000 fold [132,133].

The formation of biofilm of certain Gram-negative agents such as *Pseudomonas aeruginosa* and *Acinetobacter* species, as well as some fungal pathogens, appears to play an important role in the pathogenesis of these infections [134-137]. Aspects related to biofilm are discussed further in Chapter 6 on microbiology and Chapter 8 on prevention.

### 5.3 Catheter-related thrombosis and infection

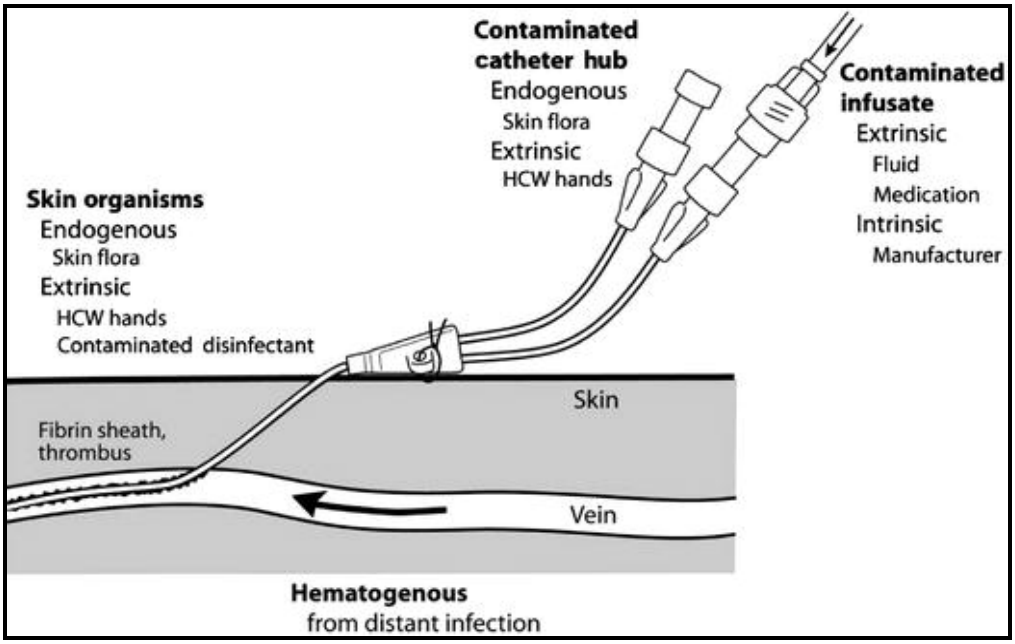
There are a number of recent studies examining the relationship between thrombosis and indwelling vascular catheters. Ultrasound studies have demonstrated that early (≤ 24 hours) catheter-related thrombosis occurs near the site of insertion and later (≥ 24 hours) thrombosis occurs near the catheter tip [138]. Peripherally inserted central venous catheters (PICCs)

appear to have a higher risk of thrombosis than centrally inserted catheters [139]. Some studies suggest that femoral catheters carry a greater risk of thrombosis as compared to subclavian catheters which themselves carry a greater risk than internal jugular catheters [140,141]. Tip position appears to even further modify the risk of thrombosis for central venous catheters, with location in the axillosubclavian-innominate veins or right atrium, posing a greater risk than superior vena cava location [142-145]. Catheter material may affect the risk with silicone having up to a threefold greater risk than other materials [146]. Data suggests that antibodies to certain coagulation factors, such as inhibitors to factors V and VIII, may increase the risk of catheter-related thrombosis through as yet, unclear mechanisms [147,148]. Bone marrow harvesting appears to induce a short-term hypercoagulable state [149]. There are some data in paediatric oncology patients that suggest that genetic risk factors such as factor V Leiden and others, may increase the risk of catheter-related thrombosis [150,151] but this seems less clear in adults [152,153].

An ongoing speculation is whether there is a link between catheter-related infection and catheter-related thrombosis, in particular, which comes first [154-157]. Such speculations have been amplified by a number of studies with heparin-coated central venous catheters, which have shown a reduction in both catheter-related thrombosis and catheter-related infection [158,159]. In these studies however, heparin is attached to the catheter via benzalkonium chloride which has antibacterial properties and may have contributed to the reduction in risk of infection. Whether the risk of thrombosis was reduced in these studies by the bound heparin, the benzalkonium chloride, or both, has not been determined. The association has assumed even greater importance following reports of a greater incidence of deep venous thrombosis associated with femoral catheterisation [140,160], which may be prevented by using heparin-bonded catheters [158,159]. In vitro studies have demonstrated that surface manipulations of polyurethane can lead to differences in protein and platelet deposition with associated

differences in bacterial adherence [161]. No in vivo data exist to show whether such observations will have clinical significance.

**Figure 1. Pathogenesis of catheter-related infections**




**HCW = health care worker**

**Adapted from Mer 2008 [5]**

## CHAPTER 6

## MICROBIOLOGY

### 6.1 Overview

The most frequent causative organisms for CRBSI are coagulase-negative *Staphylococci* (CoNS), *S. aureus*, *Enterococci* and *Candida* species [5,13,101,162-166] (see Figure 2 and Table 5).

Contaminants from the hands of medical and nursing personnel are frequently responsible for infection with such organisms as *Pseudomonas aeruginosa, Acinetobacter* species, and *Stenotrophomonas maltophilia* [5,167,100].

Emerging pathogens reported to have caused CRI include species of *Micrococcus*, *Achromobacter*, rapidly growing mycobacteria such as *Mycobacterium fortuitium* and *Mycobacterium chelonei*, and fungal organisms such as *Malassezia furfur, Rhodotorula* species, *Fusarium* species, *Trichosporin* species and *Hansenula anomala* [2,3,4,5,98,163,168].

**Figure 2**

| **The most common organisms associated with catheter-related infections** (Adapted from Mer 2008 [5]) |
|---|
| Coagulase-negative *Staphylococcus* |
| *Staphylococcus aureus* |
| *Candida* species |
| *Enterococcus* species |
| *Pseudomonas aeruginosa* |
| *Klebsiella* species |
| *Enterobacter* species |
| *Serratia marcescens* |
| *Citrobacter freundi* |
| *Bacillus & Corynebacterium* species, especially jeikeium (JK) strains |

Other organisms associated with catheter-related infections include *Bacillus* species and *Corynebacterium* species (especially JK strains). JK bacteraemia occurs almost exclusively in severely immune-suppressed patients who are, or have been, receiving broad-spectrum antibiotics and who have indwelling intravascular devices [2,3].

A concerning trend over the past few years has been the increasing rate of multidrug resistant organisms causing CRBSI, such as methicillin-resistant *S. aureus* (MRSA), fluconazole-resistant *Candida* species, vancomycin-resistant *Enterococcus faecium* and Gram-negative rods including *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter* species, which are no longer susceptible to such agents as third and fourth generation cephalosporins, ureidopenicillins, flouroquinolones and carbapenems [165,166,101].

### 6.2 Catheter-related *S. aureus* infection

*S. aureus* is a virulent pathogen that continues to cause significant morbidity and mortality in the antimicrobial era [169]. Infection of a vascular catheter by this organism may cause severe illness, with bloodstream infection and haematogenous spread to other sites resulting in serious secondary infections such as osteomyelitis, epidural abscess and endocarditis. Patients with relatively minor predisposing illness occasionally succumb to such lethal infection.

Vascular catheters have been reported to be implicated in nosocomial *S. aureus* bacteraemias in several studies [170-173]. One third to one half of all *S. aureus* nosocomial bacteraemias have been attributed to vascular catheters in these studies.

A study of nosocomial endocarditis, which excluded cases related to prosthetic valves, found that *S. aureus* accounted for 62% of cases. Causation was related to vascular catheters in 86% of cases [174].

The virulence of *S. aureus* has also been recognised in many studies of catheter-related infections [175-184].

A review of 25 studies of catheter-related *S. aureus* bacteraemia found that approximately half of the deaths in these studies were attributed to the catheter infection by the authors of the individual studies [185].

A meta-analysis of the case fatality rate associated with catheter-related infections, which included 187 studies and 3569 catheter infections, found an overall case fatality rate of 14.0% [186]. For cases of *S. aureus* catheter-related infection included in this meta-analysis, the overall case fatality rate was 18.2%. The proportion of deaths attributed to catheter infection was significantly higher for *S. aureus* than for other bacterial agents (OR 3.81, 95% CI: 2.70-5.41). A prospective epidemiologic study in a Danish hospital demonstrated a case fatality rate of 38% for nosocomial bacteraemia overall, but the case fatality rate for *S. aureus* was 65%, with 25% being attributed to catheter infection [187].

Increasing numbers of MRSA infections have been reported in recent years [54,61,162,188,189]. Knowledge about the frequency and resistance patterns of *S. aureus* is crucial as it has both therapeutic and prognostic implications.

A recent meta-analysis summarised the results of many studies of the mortality associated with MRSA, as opposed to methicillin-susceptible *S. aureus* (MSSA) bacteraemia. It found that there was significantly higher mortality with MRSA after adjusting for co-morbidity and severity of illness (OR 1.93, 95% CI: 1.54 - 2.42, $p<0.001$) [185]. This has again been most recently shown in a paper evaluating the mortality associated with MRSA infection in the ICU as part of the EPIC II study. In this point-prevalence study of infection, 13,796 adult patients in 1265 participating ICUs from 75 countries were evaluated. There were 494 patients with MRSA infections and 505 patients with MSSA infections. MRSA infection was associated with an almost 50% higher likelihood of hospital death compared with MSSA infection [190].

## 6.3 Catheter-related infections caused by coagulase-negative *Staphylococcus*

Coagulase-negative *Staphylococcus* (CoNS), particularly *S. epidermidis*, is the species most frequently isolated from infections associated with the use of vascular catheters. [1,191-196].

Traditionally CoNS have been considered avirulent microorganisms that form a major component of the cutaneous microflora. Since the 1980s, however, it has been recognised that these organisms are readily able to colonise and infect various devices used for diagnostic and therapeutic procedures such as intravascular catheters, cerebrospinal fluid shunts, prosthetic heart valves, orthopaedic devices, pacemakers, peritoneal dialysis catheters, vascular grafts and ventricular assist devices [197]. CoNS are now the leading organism for nosocomial bacteraemia [198] and it has been suggested that most of these cases are a consequence of infection of intravascular catheters [198,199]. Bacteraemia due to CoNS is associated with considerable hospital expenditures, morbidity and also an increased mortality rate. [199-201]. For problematic infections treatment options are increasingly narrowed by emerging resistance against previously active antimicrobials [202]. Over the last decades, important insight into the pathogenesis of these low-virulence microorganisms has been gained, particularly with respect to their interaction with polymer surfaces. It has now become clear that the intimate multifactorial interaction with the artificial surface is the basis for the role of these organisms in catheter-related infection [203].

### 6.3.1 Microbiology and differentiation from *Staphylococcus aureus*

Coagulase-negative S*taphylococci* are members of the family of *Micrococcaceae*. These Gram-positive, cluster-forming microorganisms are differentiated from *S. aureus* primarily by the lack of the exoenzyme coagulase (which in *S. aureus* forms fibrin by activation of thrombin). Additional markers used in the clinical microbiology workup to differentiate *S. aureus* from CoNS, are the lack of the immunoglobulin G (IgG)-binding protein A (Spa), as well as the lack of certain cell wall adhesins recognising matrix and

plasma molecules, such as the clumping factor (Clf). Moreover, CoNS do not posses certain capsular polysaccharides (Cps) specific for *S. aureus* such as the type 5/8 Cps associated with *S. aureus* invasive disease. Accordingly, for diagnostic purposes, the group of CoNS is differentiated from *S. aureus* using rabbit plasma and performing either the slide clumping test or the tube coagulase test. Several rapid commercial latex agglutination tests examining the presence of Clf, Spa and Cps are also available. Furthermore, biochemical reactions (such as mannitol fermentation) may allow laboratory technicians to distinguish between *S. aureus* and CoNS. With the use of nucleic acid amplification techniques, additional markers such as the gene for the *S. aureus* thermonuclease (alone or in conjunction with other markers such as the coagene) have been used for rapid discrimination of CoNS [192-197,204].

CoNS have been subdivided into 32 species, 15 of which have been associated with human disease. Biochemical characterisation has been the mainstay for species identification [205] and miniaturised biochemical patterns are now available for use in manual, semi-automatic, or automatic identification systems. Most CoNS involved in polymer-associated infections belong to the *S. epidermidis* group (*S. epidermidis sensu stricto, Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus warneri and Staphylococcus capitis)*. Within the *S. epidermidis* group, *S. epidermidis sensu stricto* accounts for about two-thirds of all strains [191]. In addition to members of the *S. epidermidis* group, *Staphylococcus schleiferi* and *Staphylococcus lugdunensis* [206] have also been implicated with clinical disease.

### 6.3.2 Epidemiology

Approximately 30-40% of central venous catheter-related infections are caused by coagulase-negative staphylococcal species [1,194]. Others have reported that *S. epidermidis* accounts for up to 75% of the cultured microorganisms [196]. This proportion

is irrespective of the type of catheter and includes long-term implanted as well as short-term inserted catheters, Swan-Ganz catheters, catheters used for specific purposes such as plasmapheresis or haemodialysis, or hyperalimentation catheters which have all been shown to yield CoNS, particularly *S. epidermidis* as the leading microorganism [195]. CoNS have also been increasingly isolated from the blood of hospitalised patients. This increase is thought to be in part due to an increase in line-associated CoNS infections [198].

### 6.3.3 Resistance

CoNS from nosocomial infections, particularly *S. epidermidis* are typically resistant to multiple antimicrobials, particularly the β-lactams. While almost all CoNS produce penicillinase, most clinical isolates are resistant to penicillinase-resistant penicillins as well as to all other β-lactams due to expression of *mecA* analogues conferring resistance to methicillin by production of a penicillin-binding protein (PBP2a or PBP2') with reduced affinity to β-lactams. On the basis of homology studies it has been suggested that the *mecA* gene in *S. aureus* arose from a *mecA* analogue in *Staphylococcus sciuri* [207]. Many clinical CoNS isolates are also resistant to macrolides, chloramphenicol, tetracyclines, flouroquinolones, aminoglycosides, and cotrimoxazole. CoNS species were the first *Staphylococci* with reduced susceptibility to glycopeptides such as vancomycin [208].

## 6.4 Fungal infections of catheters

During the past decade, the overall incidence of nosocomial fungaemia has continued to increase, with most cases involving *Candida* species and many such cases being related to the use of intravascular catheters.

*Candida* species have become the third most common cause of bloodstream infections among patients in intensive care units [209-211] and also represent the most common fungi isolated from intravascular devices [194]. The EPIC II Study revealed that 19% of all infections in the ICU were caused by fungi, mainly *Candida* species [212]. The type of *candida* species documented is geographically and regionally determined and may vary amongst ICUs even within the same area [209,212-218]. Although overall, *Candida albicans* remains the most dominant pathogen, an increasing number of non-albicans species have been noted over the past 15-20 years [212,214,219].

Mortality due to fungal nosocomial bloodstream infection is significant and is greater than that due to non-fungal pathogens [214,219-223].

Attributable mortalities of 35-50% are well documented [214,219,137,223].

A National Nosocomial Infections Surveillance (NNIS) analysis [221] showed that patients with fungaemia were more likely to die during hospitalisation [954 (29%) of 3256 patients] than were patients with bloodstream infection due to non-fungal pathogens [659 (17%) of 3882; relative risk (RR) 1.8; 95% CI: 1.7 - 1.9; $p<0.001$]

A relationship between candidaemia and indwelling vascular catheters has been recognised for decades. In 1962, it was reported [224] that 23 of 29 patients who developed systemic candidiasis had indwelling vascular catheters. In four of these patients, cultures from the skin around apparently uninfected cutdown sites taken at the onset of fungaemia, grew species of *Candida* that were identical to those found in the blood.

Subsequently a review of 27 cases of candidaemia revealed that 25 of the patients had indwelling central venous catheters [225]. More significantly, the authors found that 89% of these 25 patients had developed positive cultures after the central venous line had been in place for 2 weeks. CRBSI associated with C*andida* species is well documented in ICUs, burn

units, haematology-oncology patients/units, general hospitals, neonatal units and in patients receiving total parenteral nutrition [226-234]. Central venous catheterisation has been shown to be an independent risk factor for candidaemia in several studies [229,230,235].

The National Epidemiology of Mycosis Survey (NEMIS) was a prospective, multicentre study conducted at six geographically dispersed academic centres to determine rates of, and risk factors for, the development of candidal BSI among patients in surgical and neonatal ICUs. Four thousand two hundred and seventy six patients were evaluated. *Candida* species accounted for 9.2% of the total number of BSIs. More than half the *Candida* isolates recovered from the blood were non-albicans species. The mortality rate was significantly higher among patients who developed candidal BSI than among other patients (41% vs 8%; OR 7.52; 95% CI: 3.9 - 14.6; p<0.001). Of 42 patients who developed candidal BSIs 41 had a central venous catheter in place during their ICU stay prior to the development of infection. A multivariate model that included only patients who underwent surgery (n = 3201) identified an association between increased risk of candidal BSI and having had a triple-lumen catheter placed (RR 5.4; 95% CI: 1.2 - 23.6; p = 0.03) [236].

Various workers have helped add to the understanding of the capability of *Candida* species to adhere to plastic materials and cause catheter-related fungaemia. This relates largely to *Candida* biofilm and the ability, particularly of *Candida parapsilosis*, to proliferate and produce large amounts of slime. Glucose-containing solutions may be an important adjunct in the pathogenesis with work demonstrating a strong relationship between *Candida parapsilosis* fungaemia or systemic infection and hyperalimentation using intravascular devices [136,237-239].

The relevance of catheter-related fungaemia has been the subject of much debate recently particularly in the light of emerging fluconazole resistance to various isolates, as well as optimal catheter management [101,240-246].

There is the possibility that infected or colonised catheters may seed organisms to various body sites resulting in a great variety of clinical presentations depending on the affected organs. When *Candida* is disseminated, multiple organs are usually affected, including the kidney, brain, myocardium and eye (see Figure 3, Chapter 7).

Current opinion in critically ill patients is that all infected catheters should be removed where feasible [137].

Because patients with catheter-associated candidaemia who have been treated with catheter removal but without systemic antifungal therapy have developed complications such as vertebral osteomyelitis and endophthalmitis, resulting in permanent loss of vision, antifungal therapy is advocated in all cases of vascular-catheter candidaemia [247].

Other reported complications include fungal thrombophlebitis [194,248,249] and right atrial septic thrombosis [250].

### 6.5 Catheter-related infections caused by *Enterococci*

During the past decade the prevalence and importance of infections caused by *Enterococci* has increased significantly. In a prospective, observational study of 110 patients with serious enterococcal infections, such as endocarditis, bacteraemia, cholangitis, pancreatitis, osteomyelitis, pneumonia and empyema, catheter-related bacteraemia was the single most common infection accounting for 28% of all infections [251]. In infants, all infections were catheter-related bacteraemia. Overall 78% of the enterococcal isolates were identified as *Enterococcus faecalis*, 20% as *Enterococcus faecium* and 1% as *Enterococcus gallinarum* and *Enterococcus casseliflavus*, respectively. *Enterococcus faecalis* was the most common species accounting for relapse. Glycopeptide resistance among *Enterococcus faecium* is an emerging problem.

*Enterococcus casseliflavus,* a motile organism which forms yellow pigmented colonies on blood agar and reported to be associated with central venous catheter-related infection, is intrinsically resistant to low levels of Vancomycin [252,253].

### 6.6 Catheter-related infections due to Gram-negative organisms

Gram-negative bloodstream infections associated with intravascular catheters has received less attention in the literature than those associated with Gram-positive infections [254]. Similarly, the vast majority of studies investigating the pathogenesis of foreign-body infections have focused on Gram-positive organisms [255].

There is, however, an ever-increasing number of Gram-negative species causing infections related to indwelling devices [163]. Most of these are intravascular catheter-related infections caused by three major groups of Gram-negative organisms namely, members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* species. CRIs have also been reported to be caused by other Gram-negative organisms, such as rare *Enterobacteriaceae*, non-aeruginosa pseudomonads and other non-fermenting Gram-negative bacilli [25,26,165,167,256-259]. The results of several studies are summarised in Table 6.

In a prospective study Gram-negative organisms were found in 22 of 41 (54%) of colonised central venous catheters and in 6 of 11 (55%) associated bacteraemias [26]. Other investigators reported Gram-negative bacilli implicated in central venous catheter-related infection to range between 12% and 42% [25,165,256-258].

In a study evaluating 400 ICU patients with non-tunnelled CVCs, 25% of CRBSIs were caused by Gram-negative bacteria [259]. In a prospective survey to determine the rate of CRBSI among cases of primary BSI in febrile, neutropenic cancer patients with short-term non-tunnelled catheters, quantitative paired blood cultures from central venous catheters as well as peripheral vein and Bactec™ blood culture bottles were obtained to determine the

differential time to positivity [260]. Twenty seven percent of the organisms recovered were Gram-negative.

These organisms have also been implicated in the majority of hospital outbreaks of infusion-related bacteraemia. *Enterobacter* species*, Klebsiella* species. and *Serratia* species have been most frequently involved in these instances [261-266].

Gram-negative pathogens have additionally been associated with infections and bacteraemias emanating from pressure transducers used for monitoring [266,267].

Factors involved in the pathogenesis of Gram-negative infections and CRI are becoming increasingly understood.

Usually, Gram-negative bacteria adhere less readily to polymer surfaces with the exception of Pseudomonas *aeruginosa* and *Acinetobacter* species [268].

As with CoNS, the adherence properties and the formation of biofilm of *Pseudomonas aeruginosa* and *Acinetobacter* species appears to play an important role in the pathogenesis of these infections [268].

Like most environmental bacteria, *Pseudomonas aeruginosa* lives predominantly in biofilms adherent to available surfaces, from which it periodically releases planktonic (free-swimming) cells. *Pseudomonas aeruginosa* possesses a vast array of virulence factors that have been extensively reviewed [134]. Growth in biofilms protects the organism's cells from antibacterial factors produced by the host as well as from antibiotics, and may account for survival and extended persistence on foreign devices. P*seudomonas aeruginosa* embedded in thick biofilm has been seen in a variety of transcutaneous medical devices such as vascular catheters [269], peritoneal catheters [270] and urinary catheters [271]. It has been suggested that polymer catheters made of PVC or silicone may favour survival and growth of *Pseudomonas aeruginosa* [272].

Scanning electron microscope studies suggest that colonisation of polyurethane catheters with different *Acinetobacter* species may occur in a similar time frame and to an extent comparable to CoNS [268].

Possible complications of CRI due to Gram-negative organisms include sustained bacteraemia, infective endocarditis and suppurative thrombophlebitis [273] (which is most often caused by Gram-negative organisms). An emerging problem is the development of many Gram-negative agents that are multidrug resistant pathogens.

**TABLE 5 CRBSI - most common pathogens and mortality rates**

| Pathogen | Percentage of CRBSI (Rank) | | | Crude Mortality % | | |
|---|---|---|---|---|---|---|
| | Total (n = 20,978) | ICU (n = 10,515) | Non-ICU Ward (n = 10,442) | Total | ICU | Non-ICU Ward |
| Coagulase-negative *Staphylococcus* | 31.3 (1) | 35.9 (1) | 26.6 (1) | 20.7 | 25.7 | 13.8 |
| *Staphylococcus aureus* | 20.2 (2) | 16.8 (2) | 23.7 (2) | 25.4 | 34.4 | 18.9 |
| *Enterococcus* species | 9.4 (3) | 9.8 (4) | 9.0 (3) | 33.9 | 43.0 | 24.0 |
| *Candida* species | 9.0 (4) | 10.1 (3) | 7.9 (4) | 39.2 | 47.1 | 29.0 |
| *Escherichia coli* | 5.6 (5) | 3.7 (8) | 7.6 (5) | 22.4 | 33.9 | 16.9 |
| *Klebsiella* species | 4.8 (6) | 4.0 (7) | 5.5 (6) | 27.6 | 37.4 | 20.3 |
| *Pseudomonas aeruginosa* | 4.3 (7) | 4.7 (5) | 3.8 (7) | 38.7 | 47.9 | 27.6 |
| *Enterobacter* species | 3.9 (8) | 4.7 (6) | 3.1 (8) | 26.7 | 32.5 | 18.0 |
| *Serratia* species | 1.7 (9) | 2.1 (9) | 1.3 (10) | 27.4 | 33.9 | 17.1 |
| *Acinetobacter baumannii* | 1.3 (10) | 1.6 (10) | 0.9 (11) | 34.0 | 43.4 | 16.3 |

Adapted from the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) Study [165]. Data from a nationwide, concurrent surveillance study in 49 US hospitals over a 7-year period.

**TABLE 6 Gram-negative organisms and short-term CVCs, a compilation from several studies**

| Study and Reference | Haslett *(ref 258) | Yeung *(ref 257) | Gil *(ref 26) | Eyer *(ref 256) | Richet *(ref 25) | Sherertz *(ref 167) | Seifert *(ref 260) | Wispling-hof) *(ref 165) |
|---|---|---|---|---|---|---|---|---|
| Total number of isolates reported | 76 | 42 | 41 | 43 | 123 | 1032 | 22 | 20 928 |
| **ORGANISM** | **PERCENTAGE OF ISOLATES** | | | | | | | |
| Gram-negative bacilli | 22 | 12 | 55 | 42 | 26 | 28 | 27 | 31 |
| *Escherichia coli* | 0 | 0 | 5 | 6 | 0 | 14 | 17 | 6 |
| *Enterobacter* species | 29 | 0 | 10 | 33 | 6 | 16 | 17 | 3.9 |
| *Klebsiella* species | 12 | 40 | 14 | 17 | 16 | 6 | 17 | 5 |
| *Serratia* species | 6 | 20 | 19 | 0 | 6 | 7 | 0 | 17 |
| *Pseudomonas aeruginosa* | 29 | 0 | 29 | 22 | 41 | 50 | 17 | 4.3 |
| *Acinetobacter* species | 24 | 20 | 19 | 5 | 13 | 4 | 0 | 1.3 |

*ref = reference

## CHAPTER 7

## DIAGNOSIS OF CATHETER-RELATED INFECTION

### 7.1 Introduction

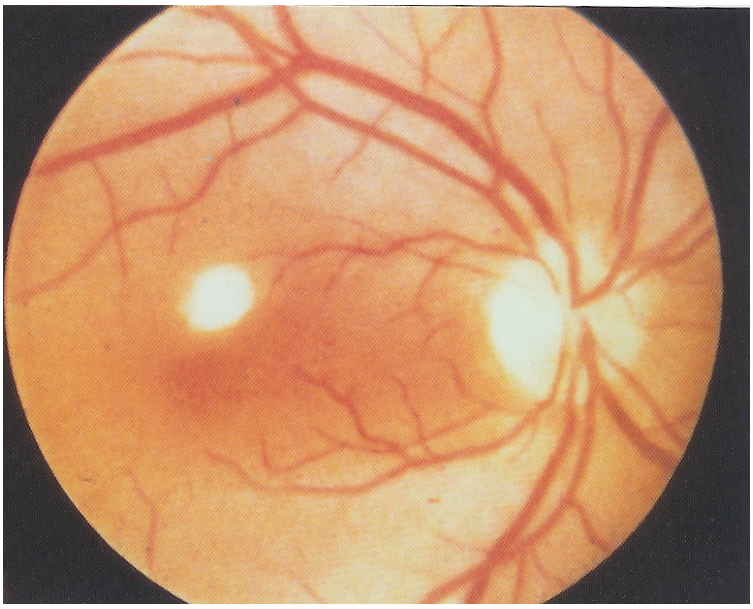
The diagnosis of CRBSI remains a major challenge [274,275] and involves both clinical and laboratory components [2,3,4,5,60,275].

Over 75% of CVCs that are removed because of suspicion of CRI are removed unnecessarily since the septic focus may be found in another anatomic site [276]. Usually, when CRBSI is suspected, the common practice in the ICU is to remove the CVC and replace it at a new site. However, only around 15% to 25% of CVCs so removed proved infected upon quantitative-tip culture [2,3,4,5,60,275-278].

### 7.2 Clinical aspects

The clinical features of CRI are generally non-specific and include fever, rigors, hypotension and confusion. If there is no apparent source of sepsis in a patient with an intravascular line, especially a central venous catheter, and if the sepsis appears to be refractory to antimicrobial therapy, or is of abrupt onset or associated with shock, the possibility of CRI needs to be considered [2,3,4,5,275-278]. Fundoscopy should always form part of the clinical examination, as focal retinal lesions are common in patients with CVC-derived *Candida* infection, even when blood cultures are negative [2,3,4,5] (see Fig 3) [5]. Contamination or purulence at the catheter insertion site is seen in less than half of the cases [2,3,4,5]. It is also not predictive of CRBSI with short-term non-cuffed CVCs [279].

**Figure 3. Candida involving retina** (Reproduced from Mer 2008 [5]



### 7.3 Laboratory aspects

In view of the non-specific clinical manifestations, microbiological evidence implicating the catheter as a source of the bloodstream infection is necessary for establishing a diagnosis of CRBSI.

The laboratory components largely revolve around culture of blood and the catheter [2,3,4,5]. A variety of methods have been studied over the past two decades, several of which have shown promising results (see Table 7). These diagnostic approaches can broadly be divided into those that necessitate catheter removal, and those that can be performed without removal of the catheter.

### 7.4 Blood cultures

Blood cultures are central to the diagnosis of CRBSI.

### 7.4.1 Peripherally collected blood

Traditionally the routine is for two to three 10ml samples, ideally from separate peripheral venepuncture sites, to be sent to the laboratory. Probable CRBSI can be diagnosed by one or more positive blood cultures obtained from a peripheral vein, when there is no apparent source for the bloodstream infection except the catheter [2,3,4,5,274,279].

Several other techniques have been described and advocated more recently.

### 7.4.2 Paired quantitative cultures

Paired quantitative cultures involve taking blood simultaneously from both the CVC and a peripheral site. Although several quantitative blood culture methods are available, one of the most widely used techniques involves placing a 10ml blood sample in an isolator tube (Isolator 10, Wampole, Granbury NJ, USA) for quantitative culturing by lysis centrifugation [280]. When the quantitative blood culture drawn from the CVC yields a colony count that is several-fold higher than that obtained from simultaneously drawn blood of the peripheral vein, the result is considered to be predictive of CRBSI. Since studies have reported different cut-off points for a positive diagnosis ranging from two-fold to ten-fold [281-285], a midpoint level whereby a colony count that is five-fold or greater from blood culture drawn from the CVC versus peripheral vein, is regarded as indicative of CRBSI [2,3,4,5]. This value has been endorsed by the IDSA (Infectious Diseases Society of America). Simultaneous quantitative blood cultures were found to be the most accurate test for diagnosis of CRBSI in a meta-analysis of studies of diagnostic tests [286]. Its use has been limited however, because it is labour intensive and expensive.

### 7.4.3 Differential time to positivity

This technique involves simultaneous qualitative blood cultures drawn through the catheter and a peripheral vein [260,287-292]. Regular blood cultures are routinely placed in an automatic culture detector that records culture positivity every 15 minutes according to changes in fluorescence related to microbial growth. Several studies indicated that definite diagnosis of CRBSI is established when the blood culture drawn from the CVC becomes positive at least 2 hours earlier than the blood culture drawn from the peripheral vein [287-289].

A meta-analysis found the pooled sensitivity and specificity for this method of diagnosing CRBSI in short-term catheters to be 89% and 87% respectively, compared with 90% and 72% respectively for long-term catheters [286]. Automated radiometric blood culture systems, in which blood cultures are continuously monitored for microbial growth, are now widely used. As a consequence, adding differential time to positivity as a routine evaluation has been advocated, as there is no additional cost or labour required [287-289].

Interpretation of this diagnostic method may be compromised if antibiotics are being administered at the time blood is drawn through the catheter. This may result in a false negative result [289].

### 7.4.4 Catheter-drawn quantitative blood cultures

Catheter-Drawn Quantitative Blood Cultures in which a single quantitative blood culture is drawn through the CVC without an accompanying peripheral blood culture can also be used to diagnose CRBSI. The threshold required for a positive diagnosis is at least 100 colony-forming units (CFU)/ml [282,293].

This method is unable to distinguish between CRBSI and high-grade bacteraemia, particularly in immuno-compromised patients with severe sepsis. Further studies are required to verify this method.

Practical and potential disadvantages to quantitative blood cultures include difficulty in aspirating blood from the catheter [294] and the dilemma of multiple lumen CVCs as each lumen may represent a source of infection. In one recent study, sampling of one out of three lumens of the catheters missed 37.3% of the CRBSI [295].

## 7.5 Catheter culture (see Table 8)

### 7.5.1 Semi-quantitative roll-plate method

The most widely used laboratory technique for culturing the catheter is the semi-quantitative roll-plate method [2,3,4,5,100] in which the catheter is removed, the distal segment of the CVC is cut and rolled against a blood agar plate at least four times, before the plate is incubated overnight [100,286,296]. Upon examination of the plate, a colony count of 15 CFU/ml, or more, is suggestive of catheter colonisation. Diagnosis of CRBSI is confirmed if catheter colonisation is associated with a positive peripheral blood culture revealing the same organisms [277,297-303]. This method is better at detecting colonisation of the external surface of the catheter rather than intra-luminal colonisation, and is therefore less sensitive for long-term catheters in which luminal colonisation more frequently leads to bloodstream infection [297,105]. This may also pertain to first generation antiseptic catheters where only the external surface of the CVC is impregnated.

However, pooled sensitivity and specificity for roll-plate catheter culture in 14 trials involving short-term CVCs were calculated to be 84% and 85% respectively [286]. Another study calculated sensitivity and specificity values for this technique of more than 90% for both short-term and long-term CVCs. However, long-term CVCs in this

study were defined as those with only seven days of dwell time or more [304]. For short-term catheter-tip cultures, the roll-plate technique is recommended for routine clinical microbiological analysis [305].

### 7.5.2 Quantitative catheter culturing techniques

Quantitative techniques for culturing the catheter include the sonication and vortexing methods, which involve extracting microorganisms from the catheter surface into a medium for culturing. This entails either flushing out the catheter segment and immersion in culture medium or placement of the segment in culture medium with sonication [167,277,306,307].

A colony count of more than 100 CFU per catheter segment is regarded as positive. The advantage of sonication or vortexing is that these methods help release microorganisms from both the external and internal surfaces of the CVC. The disadvantage is that these methods release biofilm organisms that might not be clinically relevant, whereas relevant planktonic organisms might be killed. The sonication and vortexing methods have been shown to have similar sensitivity and specificity to the roll-plate method in diagnosing CRBSI in patients with short-term CVSs [299,308]. For long-term CVCs, the sonication method was found to have higher sensitivity than the roll-plate method [105]. The pooled sensitivity and specificity of quantitative catheter segment culture for short-term catheters were 82% and 89% respectively, and 83% and 97% for long-term catheters, respectively [100,286,296]. Many microbiology laboratories do not perform quantitative blood cultures [309].

### 7.5.3 Cultures of the insertion site and catheter hub (see Table 9)

Various quantitative culture methods of the insertion site or catheter hub have been reported but have been associated with a limited specificity and positive predictive value [310-314].

### 7.5.4 Other techniques

Other techniques such as Gram stain of the catheter surface and culture of the tip in broth have been associated with high false-positive rates [3] and are now not widely used [286,296].

## 7.6 Newer techniques

Newer diagnostic methods of CRBSI infections include that of the endoluminal brush [4,5,315,316] and the Gram stain and acridine orange leucocyte cytospin test (AOLC) [4,5,20,317,318].

**7.6.1 The endoluminal brush** is a tapered nylon brush on a steel wire that is passed through the catheter hub and lumen, withdrawn, and immediately placed in a buffered container. This container undergoes sonication and vortexing after which the solution is cultured onto blood agar plates. Counts of greater than 100 CFU/ml are deemed positive [315]. This technique is based on the premise that bacteria adhere to the fibrin sheath on the inner surface of the CVC and fibrin becomes enmeshed in the brush's bristles. High sensitivities and specificities have been reported with this technique [315] which does not require sacrifice of the catheter, but there is still a delay before culture results are known [4]. There is also a concern that the process of brushing may lead to embolisation of biofilm as well as other side effects such as arrhythmias [286,296,319].

The place of the endoluminal brush in clinical practice is still to be fully determined but at present is not widely used and further studies are required [4].

**7.6.2 The Gram stain and AOLC test** (see Table 10) [320] is a recently described method for rapidly diagnosing CRBSI without catheter removal within one hour. The test is performed on blood samples drawn from the CVC and has been reported to have high sensitivities and specificities. A negative predictive value of 97% and a positive predictive value of 91% have been reported for the diagnosis of bacteraemic CRI [315]. This promising technique compares favourably with other diagnostic methods, particularly those that require removal of the catheter and may permit early targeted antimicrobial therapy, or conversely avoid unnecessary use of antibiotics [4,5]. Although cost-efficient and simple, this test has not been widely used at present, but may represent a promising way of establishing the diagnosis of CRI in the future. The theoretical risk of toxicity of acridine-orange, an intercalating agent, may be a factor that has resulted in some precautions in microbiology laboratories.

### 7.7 Novel techniques

Potentially innovative techniques include a **serological test for the diagnosis of CRI due to coagulase-negative staphylococci** [321].

In a study evaluating this test, the authors compared 67 patients suspected of having CRI due to CoNS and 67 control patients with a CVC, but without CRI. Ten millilitres of blood were obtained in both groups and serum antibody levels of both IgG and IgM against a short-chain lipoteichoic acid antigen isolated from CoNS were determined, using an enzyme linked immunosorbent assay (ELISA) technique. Significant differences between the mean IgG and IgM titres of the test group and the control group were observed. Using an IgG titre of 20,000, the test had a sensitivity of 70% and a specificity of 90%. Similar results have subsequently been reported in a study published by the same group [322]. Further studies are however needed before such serological tests can be proposed as routine. The usefulness of serological methods for the diagnosis of CRI remains to be confirmed.

### 7.8 Other tests

Various other tests that have been proposed, such as **C-reactive protein** and **introblue tetrazolium tests**, have not proved to be useful in the diagnosis of CRI [283,323,324].

### 7.9 Current suggestions

In addition to appropriate clinical evaluation, one of the following microbiological methods to confirm the diagnosis of CRBSI is currently suggested [305,325].

1. Positive semi-quantitative or quantitative culture of the catheter,
2. Simultaneous quantitative blood cultures drawn through the CVC and peripheral vein with a ratio of 5:1 or more (CVC versus peripheral), or
3. Differential time to positivity.

## TABLE 7

## Microbiological diagnostic methods of catheter-related bloodstream infections

| | Diagnostic criteria | Accuracy | | Comments |
|---|---|---|---|---|
| | | Sensitivity | Specificity | |
| **Techniques without CVC removal** | | | | |
| Simultaneous quantitative blood culture | Quantitative blood culture drawn through CVC yields CFU count five-fold higher or more than CFU count from simultaneously drawn blood from peripheral vein | 93% [286] | 97-10% [286] | Found to be most accurate test for diagnostic CRBSI in a meta-analysis [286] |
| Differential time to positivity | Blood culture drawn from CVC becomes positive ±2 h before simultaneously drawn blood culture from peripheral vein | 89-90% [286] | 72-87% [286] | Concurrent antibiotic administration may interfere with result. Cost effective |
| CVC-drawn quanti-tative blood culture | Quantitative blood culture from CVC is >100 CFU/ml | 81-86% [286] | 85-96% [286] | Cannot differentiate between CRBSI and high-grade bacteraemia |
| Acridine orange leucocyte cytospin followed by Gram stain | Presence of any bacteria | 96% if followed by Gram stain [317] | 92% if followed by Gram stain [317] | Promising |
| Endoluminal brush | Quantitative culture with >100 CFU/ml | 95% [315] | 84% [315] | May induce bacteraemia, arrhythmia, embolisation |
| **Techniques requiring CVC removal** | | | | |
| Semiquantitative CVC tip culture, roll plate | ≥15 CFU/ml from CVC tip | 45-54% [286,297,105] | 85% [286,297,105] | Recommended test for short-term catheter tip cultures for routine clinical, microbiological analysis |
| Quantitative CVC culture centrifugation, vortexing, sonication | ≥103 CFU from CVC tip | 52-83% [286] | 89-97% [286] | Not performed in many microbiology laboratories |

CVC = central venous catheter
CFU = colony forming units
CRBSI = catheter-related bloodstream infection

**TABLE 8 Methods of catheter-tip culture**

**Semi-quantitative catheter-tip culture method** [100]

At the time of catheter removal, any antimicrobial ointment or blood present on the skin around the catheter should be removed. The catheter is withdrawn with sterile forceps, the externalised portion being kept directed upward and away from the skin surface. For short peripheral catheters, the entire length is aseptically amputated and cultured. For longer catheters, the distal 5 to 7 cm catheter segment is sectioned and cultured. Catheter segments are transported to the laboratory in a sterile tube. In the laboratory, the catheter-tip segment is transferred to the surface of a 10 cm, 5% sheep-blood agar plate for semi-quantitative culturing. While downward pressure is exerted with a flamed forceps, the catheter is rolled back and forth across the surface at least four times. Plates are subsequently incubated at 37°C. All colony types appearing on the plate are enumerated, and all organisms recovered are fully identified.

**Quantitative tip-flush culture technique** [306]

The intradermal segment is separated from the intravascular catheter segment. A needle is inserted into the proximal end of the intravascular segment, which is immersed in 2 ml or 10 ml of trypticase soy broth, depending on the size of the insert, and flushed three types. The broth is serially diluted 100-fold, and 0.1 ml of the dilution is streaked onto blood agar. After incubation, the number of cfu is calculated by multiplying the number of colonies by 10 times the dilution factor, and dividing by the volume of broth in which the insert has been immersed.

**Quantitative culture technique after catheter vortexing** [326]

After removal, the distal 5 to 6 cm catheter segment is sectioned in a sterile tube. One millilitre of sterile water is dripped onto the catheter and the tube is vortexed for 1 minute, then 0.1 ml of the suspension is sampled and plated over a 5% horse-blood agar plate. The plate is incubated at 37°C and examined daily for 5 days. All colony types are identified by colony morphology, Gram stain, and standard microbiologic techniques. The colonies are enumerated, and the counts are corrected for the initial 1/10 dilution.

**Quantitative culture technique after catheter ultrasonication** [167]

After removal, the catheter tip is placed in 10 ml of tryptic soy broth, sonicated for 1 minute (55,000 Hertz, 125 Watt), and then vortexed for 15 seconds. A 0.1 ml sample of the broth is added to either 0.9 ml (1:10 dilution) or 9.9 ml (1:100 dilution) of saline and vortexed. Then, 0.1 ml of these dilutions and 0.1 ml of the sonicated broth are surface-plated, using a wire loop on blood agar.

**TABLE 9 Methods of skin and hub cultures**

**Culture of the skin at the catheter insertion site** [299,327,328,329]

Cutaneous specimens may be obtained with a dry or a moistened swab, after removal of the dressing. No antiseptic agent is needed. The cotton swab may be moistened with 0.01 M phosphate-buffered saline (PBS), using the blister of the device. The swab may then be rubbed on the skin in two perpendicular directions on a predefined area surrounding the insertion point of the catheter (eg. 2 x 2 cm, or 6 x 4 cm; a template may be used). Other authors propose to swab the sterile cotton applicator from top to bottom in 10 back-and-forth strokes, in the predefined area, followed by a second set of 10 back-and-forth strokes at right angles to the first. The cotton swab is then pulled back into the protective tube which contains 1.0 ml of PBS, and vortexed for 90 seconds. In the Culturette® system, 0.5 ml of a Stuart medium is used. Finally, a 0.1 ml sample of this solution (and eventually a 1:100 solution of this solution) is plated on blood agar, and colonies are counted after incubation for 24 and 48 hours at 35ºC.

**Culture of the catheter hub** [103,299,313,328]

The catheter is clamped in order to avoid any blood contamination, and the luer lock is removed aseptically. After cleaning the outside of the hub with a disinfectant, the inner hub sample is taken using a swab that is introduced into the hub and rubbed repeatedly against its interior surface. The hub is then streaked onto an agar plate for semi-quantitative culture.

**TABLE 10 Method of the Gram stain and acridine-orange leucocyte cytospin (AOLC) test [320]**

A 1 ml sample of blood (treated with edetic acid) is aspirated from the catheter lumen for the Gram stain and AOLC test, which require two 50 µl samples of catheter blood. Each sample is placed into 12 mm by 75 mm polystyrene tubes to which is added 1.2 ml formalin (10% by volume) saline (0.025 mol/l) solution, and the mixture left for 2 minutes. 2.8 ml 0.19 mol/l saline is then added to each tube, followed by centrifugation at 352 g for 5 min. The supernatant is decanted and the cellular deposit is homogenised by vortexing for 5 seconds and then transferred to a cytospin capsule that contains a microscope slide. The cellular suspension is centrifuged at 153 g for 5 minutes in a cytocentrifuge. A monolayer of leucocytes and microorganisms is placed on each of two microscope slides, which are heat-dried on a 60°C hotplate for 3 minutes and then stained with either 1 in 10,000 (weight/volume) acridine-orange or Gram stain and viewed by ultraviolet and light microscopy. A minimum of 100 high-power fields are examined, and the presence of any microorganisms within the cellular monolayer (on either slide) is considered a positive result.

## CHAPTER 8

## PREVENTION OF CENTRAL VENOUS CATHETER-RELATED INFECTION IN THE ICU

Because of the difficulties in treatment of catheter-related infections, their impact on morbidity and mortality, and significant additional costs, prevention of CRI remains a major goal in modern medicine. In most cases, CRBSIs can be prevented or limited.

Strict adherence to handwashing and aseptic technique remains the cornerstone of prevention of CRI [2,3,4,5,20,21,82]. Several other measures have been reported to confer additional protection, some of which need to be considered in the preventive strategy. These are described below.

### 8.1 Staff education

Education and training of health-care providers who insert and maintain CVCs has been shown to be successful in preventing catheter-related infection, improving patient outcomes and reducing healthcare costs [330]. The experience of the operator is important with the risk of infectious complications being inversely proportional to experience and operator skills. Catheterisation by less-experienced providers is associated with a higher risk of infection [331]. Education regarding appropriate catheter insertion technique has been shown to significantly improve patient outcomes, and simulation-based training programmes have also been demonstrated to be useful [332,333]. Programmes focusing on nurses' catheter care have been associated with a reduction of catheter-related infection in the USA [334]. Educational initiatives that have included interns, ICU nurses, residents and consultants have also been associated with a sustained reduction in CRBSI in both surgical and medical ICUs.

A didactic education programme and "hands on" demonstration of insertion of both CVCs and arterial lines to beginner physicians in training resulted in a steady and significant reduction in

CRBSI and primary bloodstream infection over time [333]. Such educational interventions appear to be lacking or are not adequately adhered to in limited-resource countries [77].

Although educational programmes can be helpful in reducing CRBSI, compliance to individual elements of the programme may wane over time and continuous and repetitive re-enforcement of the principles is usually necessary [15,335,336].

Nursing staff reductions below a critical level may contribute to increased catheter-related infection by making adequate catheter care difficult [337]. A four-fold greater risk of catheter infection has been reported when the patient-to-nurse ratio was doubled [338]. The replacement of regular nurses by floating or agency nurses has also been shown to increase the risk of device-related infections [339]. These studies highlight the need for appropriately trained nurses in sufficient numbers and ongoing and repetitive education is necessary for optimal catheter care in the ICU [337].

### 8.2 Infusion therapy teams

A number of studies have shown that catheter insertion and catheter maintenance by a team of specially trained physicians, technicians and nurses is associated with a lower risk of CRI. Such infusion therapy teams have been associated with reductions of CRBSI of up to 8-fold and also limit overall costs [334,340-344]. Similarly, strict adherence to protocols for catheter insertion in the ICU, wards and operating theatre also decreases the rates of CRI [3,4,5,20].

### 8.3 Maximum sterile barriers

Careful hand washing together with full barrier precautions including the use of mask, cap, sterile gloves, gown and large sterile drape have been shown to significantly reduce the risk of CRI and CRBSI [97,345]. This practice has been associated with a greater than 6-fold decrease in CVC-related sepsis and cannot be over-emphasised [5].

Strict asepsis at the time of insertion is a crucial step for effective infection control. The use of maximum sterile barrier precautions has been shown to be cost-effective [345]. The standard practice in the 1980s and early 1990s included only the use of sterile gloves and small drape when inserting CVCs.

The benefit of using maximal sterile barrier precautions to reduce the risk of CRI has been elucidated in two studies. In one study it was shown that the use of masks, caps, sterile gloves, gowns and a large drape that covers the patient during insertion of non-tunnelled non-cuffed central venous catheters leads to a greater than 6-fold reduction in CRBSI, compared to a control group in which only sterile gloves and small sterile drapes were used [345]. In the other study, on Swan-Ganz pulmonary artery catheters, the application of such barrier precautions was associated with a 2-fold lower risk of infection [97].

Other observational studies have supported these findings. It is concluded that these measures are cost-effective, beneficial to the patient and thus strongly recommended [346].

### 8.4 Skin antisepsis

The density of microorganisms at the catheter insertion site is a major risk factor for CRI and cutaneous antisepsis is regarded as one of the most important measures for preventing CRI and CRBSI [5,75]. A variety of skin antiseptics, most notably 10% povidone iodine, 70% isopropyl alcohol, and alcoholic or aqueous chlorhexidine (2%, 1%, 0.5%, 0.25%) have been studied. Their respective efficacy in preventing catheter colonisation and bloodstream infections has been compared in various trials.

A meta-analysis of eight randomised trials comparing chlorhexidine to aqueous povidone iodine and involving 4143 short-term catheters, the bulk of which were CVCs, revealed that aqueous or alcoholic chlorhexidine solutions were superior to aqueous povidone iodine and significantly reduced catheter colonisation CRBSI [337,347]. Catheter insertion sites and duration

of catheterisation were comparable between the two groups. Chlorhexidine solutions were either an aqueous solution of 2% chlorhexidine (2 trials), a 70% alcoholic solution of 0.5% chlorhexidine (4 trials), an alcoholic solution of 1% chlorhexidine (1 trial) or a combination of 0.25% chlorhexidine, 0.025% benzalkonium chloride and 4% benzyl alcohol (1 trial).

Chlorhexidine preparations were associated with a reduction of CRBSI by approximately 50% (RR:0.51 [95% CI, 0.27 - 0.97]). Extrapolation of this data suggests that for every 1000 catheter sites disinfected with chlorhexidine solutions, 71 episodes of CVC colonisation and 11 episodes of infection would be prevented.

Similar findings with an alcoholic formulation of 2% chlorhexidine for skin antisepsis with CVCs has also been reported [348]. The use of chlorhexidine for skin antisepsis also appears to be cost-effective. In a study evaluating the economic benefits of chlorhexidine gluconate compared with povidone iodine for vascular catheter site care, the use of a chlorhexidine skin preparation resulted in an economic saving of $113 per catheter [349].

The superiority of chlorhexidine in the bulk of these studies has been explained, at least in part, by a synergistic effect with alcohol, even for low chlorhexidine concentrations [337]. This synergistic effect has also been demonstrated with povidone iodine, and is based on a randomised multicenter crossover trial comparing the effectiveness of two pre-insertion cutaneous antiseptic protocols using aqueous 10% povidone iodine or a solution of 5% povidone iodine in 70% ethanol [350]. Catheter colonisation and CRI rates were significantly lower in patients who were managed using the alcohol povidone iodine solution compared with the aqueous povidone iodine solution protocol (no significant effect was seen on bloodstream infections but the study was underpowered to explore this issue).

A recent trial has compared a chlorhexidine-based solution to 5% alcoholic povidone iodine for central venous catheter care. A total of 538 catheters were randomised, of which 481 (89.4%) produced evaluable culture results [351]. The chlorhexidine-based solution was

associated with a significant reduction in the incidence of catheter colonisation (50%) (11.6% vs 22.2%, p=0.002; incidence density 9.7 vs 18.3 per 1000 catheter days). The use of the chlorhexidine-based solution was also associated with a trend toward lower rates of catheter-related bloodstream infection (1.7% vs 4.2%, p=0.09; incidence denity 1.4 vs 3.4 per 1000 catheter days).

Chlorhexidine-based solutions currently appear to be more effective than povidone iodine, even in alcoholic formulation, and should be the recommended first-line antiseptic for CVC care.

The potential role of antiseptic combination has been tested in one monocentre randomised controlled trial. A 1-minute application of propanol/chlorhexidine followed by a 1-minute application of povidone iodine (4.7%) was found to significantly decrease catheter colonisation as compared with 2-minute povidone iodine (24.4%) or 2-minute propanol/chlorhexidine (30.8%). The potential benefit of this combination requires further study [352].

It is the practice in the multidisciplinary adult ICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) to use a chlorhexidine gluconate-containing solution for skin preparations [5].

Tolerance to chlorhexidine-based solutions is generally excellent. Contact dermatitis and, exceptionally rarely, anaphylactic reactions have been reported (less than 100 cases globally).

### 8.5 Antibiotic prophylaxis

No studies have demonstrated a reduction in CVC infection rates with oral or parenterally administered antibacterial or antifungal agents given at the time of catheter placement [140].

Several studies have, however, reported that antibiotic administration in patients with a CVC in situ reduces the risk of catheter colonisation and CRBSI [140].

Systemic antibiotic prophylaxis should not be used during catheter placement or maintenance for the purpose of preventing catheter infection [337].

### 8.6 Luminal antimicrobial flushes and lock solutions

Luminal antimicrobial flushes and lock solutions have also been used in selected cases in some units with variable success, but are currently not routinely recommended [60].

Many antimicrobials such as vancomycin, teicoplanin, daptomycin, gentamicin, cephalosporins, minocycline-EDTA and alcohol (at a concentration ranging between 25% and 40% ethanol), ciprofloxacin, linezolid, tigecycline, and taurolidine have been tested for lock therapy, with interesting results [5,60,353-362].

Antimicrobial lock solutions consist of 2ml of an antimicrobial drug often mixed with an anticoagulant, which is needed to fill the lumen of the catheter. A few studies have independently shown a significant reduction of CRBSI associated with the use of vancomycin and heparin lock solution [363,364] although others have failed to show significant benefit [365,366].

In view of the limited activity of vancomycin against staphylococci embedded in biofilm, further data derived from large prospective studies are required to address concerns regarding vancomycin resistance associated with vancomycin-containing catheter lock solutions [358]. Chelators such as EDTA (edetic acid) or citrate have an anticoagulant activity similar to heparin and have been found to enhance the activity of antimicrobial drugs against organisms embedded in biofilm [354,355,356,367]. Heparin has been used widely as an antithrombotic agent in catheters and the reduction in thrombus formation has been reported to reduce catheter infection [31]. More recently, it has been shown that saline is as effective as

heparin in maintaining catheter patency [368,369]. Of note, recent work has shown that heparin, and to a lesser extent saline, enhances staphylococcal biofilm formation [370].

Ethanol lock solutions have been evaluated in several studies. Two hours of exposure to 70% ethanol is sufficient to kill established biofilm of gram-positive, gram-negative and *Candida* species in vitro [371], and has been used to treat persistent bacteraemia in long-term intravascular devices [372]. It is effective at concentrations greater than 20% and inhibits the biofilm formation even if left in place for a period of just two minutes (>50% ethanol) [373]. No interactions with catheter structure have been noted with these concentrations. An initial randomised controlled trial comparing a daily instillation of lock for a two-hour dwell time of prophylactic 70% ethanol lock versus heparinised saline in haematological patients, found a statistically significant reduction of CRBSIs (p=0.003) [374]. A very recent subsequent randomised controlled trial involving 379 adult haematology patients failed to confirm these encouraging results. This study utilised a 15 minute-daily 70% ethanol lock versus control. Various side-effects were noted with the flush of the ethanol lock including dizziness (50%), altered taste (40%) and facial flushing (40%) [375]. However, a small retrospective study in paediatric patients receiving total parenteral nutrition, revealed that a 70% ethanol lock regimen instilled three times per week significantly decreased the rate of CVC infections. No serious adverse reactions were noted during ethanol lock therapy [376].

A large French randomised double-blind, controlled trial comparing a two minute 60% ethanol lock to saline on haemodialysis catheters in ICU patients is currently underway. The study will involve twelve hundred patients. Eight hundred patients have already been enrolled [377].

### 8.7 Tunnelling of CVCs

This involves placing the proximal segment of the catheter under the skin at a distance from the point of entry to the vein. A meta-analysis of randomised controlled trials demonstrated that tunnelling decreased catheter colonisation by 30% and bloodstream infection by 44%,

compared to non-tunnelling [378]. A subsequent study in critically ill patients reported a lower rate of CRBSI [379]. Despite these results, routine tunnelling of CVCs for short term use is not widely practiced.

### 8.8 Silver-chelated subcutaneous collagen cuffs

These cuffs may be attached to percutaneously inserted CVCs and are designed to act as both a mechanical barrier to the migration of microorganisms as well as an antimicrobial deterrent (through the effects of silver ions). They have been shown to lower the risk of catheter colonisation and CRBSI in critically ill patients [380,381]. The anti-infective effect is short-lived, however, as the collagen to which the silver ions are chelated is biodegradable. Other drawbacks include cost and the need for specialised training [4].

### 8.9 Antiseptic hubs

These have been designed to protect against hub colonisation. Initial work demonstrated a four-fold decrease in catheter-related sepsis with their use [382]. A major limitation, however, is that protection is only conferred against organism migration along the internal surface of the catheter. They do not protect against migration of skin organisms along the external surface. A subsequent randomised trial involving 130 catheters failed to show a protective effect [383].

### 8.10 Catheter insertion site

The location at which a catheter is inserted has been reported to influence the subsequent risk of catheter-related infection, largely related to the differences in density of local skin flora as well as the risks of thrombophlebitis [337].

A significant number of randomised prospective trials and observational studies indicate that the use of the femoral insertion site is associated with a higher risk of catheter colonisation and CRBSI as compared to the jugular and subclavian sites [101]. A randomised study involving 270 catheters inserted in the femoral or subclavian veins of ICU patients, found that the

femoral catheters had a much higher rate of significant colonisation compared to CVCs in the subclavian position (RR: 6.4 [95% CI: 1.9-21.2]). In addition, there was a trend toward a higher rate of CRBSI in the patients instrumented with a femoral catheter [140]. Most prospective observational studies have reported similar findings [384]. Some of the increased risk of infection may be related to body habitus [385]. Use of the femoral site is also associated with a greater risk of thrombus [386], and the association between thrombus and infection has been well documented [155] and previously alluded to.

A meta-analysis of three prospective non-randomised studies compared catheters inserted in the internal jugular (n = 275) and subclavian (n = 429) veins. The use of the internal jugular vein was associated with an increase in the risk of bloodstream infections compared to the subclavian route (RR: 2.24 [95% CI: 0.2-22.1]). Multivariate analysis of several prospective studies has shown more frequent infectious complications when using femoral or internal jugular access [387]. The subclavian site of insertion is reported to be associated with a lower risk of colonisation and infection compared to the internal jugular and femoral sites [388,389,390]. A prospective observational study evaluating internal jugular vein versus subclavian vein catheters revealed a two-fold increase in CRBSI when catheters were inserted in the internal jugular vein [391]. Post hoc analyses using multivariate regression of randomised prospective studies evaluating the effectiveness of anti-infective catheters, have shown that the subclavian insertion site is associated with the lowest rate of significant catheter colonisation [392,393]. As a consequence of this data, the subclavian site is often suggested as the preferred site for catheter insertion in adults, including in many guidelines [1,394-396].

Factors to consider when choosing the anatomic location for CVC placement include the potential for mechanical complications such as pneumothorax, risk of subclavian vein stenosis, location of pre-existing catheters, presence of anatomic deformities, risk of bleeding and familiarity with the procedure (catheter-operator skill) [30,32]. In paediatric patients, the

femoral route has been associated with fewer mechanical complications and an infection rate equivalent to that of non-femoral access [397,398].

In a recently published study from Johannesburg in critically ill patients, the site of CVC insertion (internal jugular vein versus subclavian vein) was not noted to be a risk factor for catheter infection [21].

### 8.11 Ultrasound guided placement of CVCs

The use of ultrasound is gaining widespread popularity in the critical care setting for a number of indications, including guidance for CVC placement, particularly in the internal jugular vein position. In this technique an ultrasound probe is used to localise the vein and to measure the depth beneath the skin. An introducer needle is then guided through the skin and into the vessel. The location of the vein with ultrasound decreases the number of puncture failures and complications, such as arterial puncture, and reduces time for catheter insertion [399]. In a meta-analysis of eight studies, the use of bedside ultrasound for the placement of catheters in the internal jugular vein substantially reduced mechanical complications compared with the standard landmark placement technique (RR: 0.22; [95% CI: 0.10 - 0.45]) [400]. Data for subclavian and femoral veins are encouraging but limited [337].

Fewer mechanical complications and reduced number of attempts at catheterisation may translate into a lower risk of CRBSI. In a randomised study with 900 ICU patients, ultrasound-guided placement resulted in a reduction in bloodstream infection (10.4% vs 16.0%, $p < 0.01$) [401]. Where ultrasound equipment is available and physicians have been formally trained, ultrasound guidance should be utilised before CVC placement is attempted. This technique appears to be a useful adjunct to limit mechanical complications and infection [402].

### 8.12 Catheter site dressings

There has been an ongoing debate concerning the best method of catheter dressing. This has essentially revolved around the relative merit of gauze versus transparent films. In a meta-analysis of catheter dressing regimens, CVCs on which a transparent dressing was used were associated with a significantly higher incidence of catheter tip colonisation but a non-significant increase in CRBSI [403]. Accumulation of moisture under these dressings has been associated with increased microbial contamination at the insertion site [404-406].

The development of new transparent, polyurethane dressings with high permeability and increased water vapour transmission rates, thus allowing no penetration of moisture and microbes from the outside, but permitting the evaporation of water vapour, has reduced the risk of moisture build-up under the dressings [407]. These newer transparent dressings have become a popular way of dressing catheter insertion sites because they allow continuous visual inspection of the site, allow patients to have baths, and to shower without saturating the dressing. There is, however, no evidence whether the newer transparent dressings provide better protection against infection as compared to gauze dressings. Gauze dressings have been advocated as possibly being preferable if blood is oozing from the catheter insertion site or if the patient has profuse perspiration [402].

Various guidelines recommend the use of either transparent or gauze dressings [1,394,395]. Others prefer sterile, transparent, semi-permeable polyurethane dressings [402] or gauze dressings [20,83]. Early work with a chlorhexidine-impregnated hydrophilic polyurethane foam dressing has been reported to be associated with a reduction in CVC-related infection [4,5,408]. The Biopatch™ antimicrobial dressing (Johnson & Johnson, USA) is a hydrophilic polyurethane foam dressing impregnated with chlorhexidine gluconate, designed to release chlorhexidine and to inhibit microbial growth at the catheter entry site for at least seven days.

These patches are affixed around the newly inserted catheters, pressed firmly onto the skin and covered with a transparent dressing. A recent meta-analysis [409] that included eight randomised controlled trials demonstrated that chlorhexidine-impregnated sponge dressings are associated with a reduction in vascular and epidural catheter exit site colonisation (14.8% vs 26.9%, OR 0.47, 95% CI: 0.34-0.65; overall 14.3% vs 27.2%, OR 0.40, 95% CI: 0.26-0.61; p<0.0001) but no significant reduction in CRBSI (2.2% vs 3.8%, OR 0.58, 95% CI: 0.29-1.14, p=0.11).

The protective effect may be more pronounced in patients that are immunosuppressed. In a study involving 601 oncology patients receiving chemotherapy, the incidence of CRBSI was reduced in patients receiving the chlorhexidine-impregnated sponge compared to standard dressing (p=0.016, RR 0.54, CI 0.31-0.94) [410].

In a prospective, randomised blinded study performed in seven ICUs and involving 1636 patients and 3778 catheters, the chlorhexidine-impregnated sponge was associated with a lower rate of catheter colonisation and CRBSI even when the background rate of infection was low [411]. There was no evidence of increased bacterial resistance at the site of insertion and the chlorhexidine-sponge dressing was well tolerated. Potential drawbacks of the chlorhexidine-impregnated sponge include the risk of local contact dermatitis, and that it may obscure visual inspection of the catheter entry site.

Currently, the preference in the multidisciplinary adult ICU at CMJAH is to use an adhesive gauze dressing with a central non-adherent pad following prior appropriate administration of a chlorhexidine gluconate-containing solution to the insertion area. This form of dressing does not stick to the catheter and therefore limits manipulation of the catheter when the dressing is removed. It also provides excellent absorptive and adsorptive properties, minimising moisture retention around the catheter insertion site and the potential for microbial growth [4,5,20]. The optimal frequency for routinely changing catheter dressings is unknown. Replacement of the

dressing is suggested by most authorities as being necessary if it has become damp, loosened or soiled [1]. More recently, it has been suggested that there may be little benefit to changing the dressing before seven days [411].

It is currently the policy in the CMJAH to change dressings daily. This allows for inspection of the insertion site, which is cleaned with a chlorhexidine gluconate-containing solution in a sterile fashion. Cleaning includes removal of old blood clots, exudates and crusts. A chlorhexidine gluconate-soaked piece of sterile gauze is then applied to the insertion site for approximately 30 seconds, before drying and dressing the area. Any signs of local infection (red, hot, painful, purulence) is reported and documented [2,3,4,5,20].

### 8.13 Needleless connectors

Needleless intravascular catheter systems were introduced in the early 1990s to reduce the risk of needlestick injuries to health care workers and biological contamination. A concern is that, if not handled properly, these connectors have been shown to increase the rate of CRBSI [402]. When these devices are used, it has been suggested that the risk of contamination should be minimised by decontaminating the access port before and after use with a 70% alcoholic solution or a chlorhexidine gluconate solution [101,402]. Among the available devices, split system valve designs are preferred over positive pressure mechanical valves because they are associated with a lower risk of CRBSI [412,413].

### 8.14 Topical antimicrobials

In an attempt to minimise the risk of microbial colonisation spreading from the insertion site along the catheter surface, topical antimicrobials have been applied. A lower rate of CRBSI has been associated with the use of PNB (polymixin-neomycin-bacitracin) at the skin entry site. However the overall protective effect is offset by a higher risk of fungal colonisation and infection [2,3,414].

Mupirocin which is mainly applied for the eradication of methicillin-resistant *S. aureus* in nasal carriers, has also shown some success in the reduction of catheter-related infection, used either as local treatment or to eradicate nasal staphylococcal carriage in haemodialysis patients [415-417]. However, prolonged use of mupirocin ointment may lead to the development of mupirocin resistance in both CoNS and *S. aureus* [418,419].

Studies with other ointments have demonstrated conflicting results [420,421]. In general, the routine application of topical antimicrobials on the catheter site is not recommended [402].

### 8.15 In-line filters

To minimise the risk of catheter related infection due to extrinsic contamination by the infusate, in-line filters with a pore size of 0.22 - 0.45µg have been proposed as a means of retaining bacteria and endotoxins [422,423.] They have also been associated with a reduction in the incidence of infusion-related phlebitis [424,425]. Most however, are not able to prevent the passage of endotoxins. They have to be changed frequently and may become blocked, leading to an even higher risk of contamination. In view of their doubtful benefit in minimising catheter related infection and relatively high cost associated with their use, they are not currently recommended for routine use to prevent CRI [1,61,394].

### 8.16 Peripherally inserted central venous catheters (PICCs)

PICCs provide an alternative to subclavian or jugular vein catheterisation and are inserted into the superior vena cava or right atrium via the cephalic and basilic veins of the antecubital fossa by “blind” percutaneous cannulation [3,4,5], or in the mid-arm by ultrasound guided cannulation of the basilic, brachial or cephalic vein. The results of ultrasound technique are optimal if used in conjunction with the micro-introducer technique [402]. PICCs are 50-60cm in length and usually made of silicone and polyurethane. Compared with other non-tunnelled

short-term CVCs, they have traditionally been associated with few mechanical complications, an apparent lower rate of infection, and decreased cost [4,20,426,427].

PICCs are apparently associated with a lower risk of infection, most probably because of the exit site on the arm, which is less prone to be contaminated by nasal and oral secretions [401]. In a recent multicentre study analysing 2101 central venous catheters inserted in critically ill patients, PICCs were associated with a significantly lower rate of bloodstream infection than standard CVCs [428]. No randomised control study has yet proven this.

A meta-analysis including 48 papers published between 1979 and 2004, did not find conclusive evidence that PICCs are superior to CVCs in acute care settings [429]. In this meta-analysis infectious complications did not significantly differ between PICCs and CVCs. All papers included in this analysis reported experience with PICC inserted with the “blind” technique, and not by ultrasound guidance, which is the preferred method for PICC insertion [429]. Additional recent work has demonstrated that PICCs are associated with a rate of CRBSIs similar to that of conventional CVCs placed in the internal jugular or subclavian veins [5,430].

It has been suggested that it is reasonable to consider PICC insertion for patients with severe anatomical abnormalities of neck and thorax which may be associated with difficult positioning and nursing of a centrally placed CVC, in patients with very low platelet counts, possibly in those with tracheostomy and in patients who are candidates for home parenteral nutrition for limited periods of time [401,402]. PICCs are not advisable in patients with renal failure and impending need for dialysis, in whom preservation of upper-extremity veins is needed for fistula or graft implantation. The assumption that PICCs are safer than conventional CVCs with regard to the risk of infection is in question and a larger, adequately powered randomised trial that assesses peripheral vein thrombophlebitis, PICC-related thrombosis, premature dislodgement and CRBSI has been advocated [430].

### 8.17 Catheter material

Teflon or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene [431-434]. A study evaluating the contribution of vascular catheter material to the pathogenesis of infection, demonstrated an increased risk for infection also with silicone catheters [45]. The majority of catheters sold in the developed world are no longer made of polyvinyl chloride or polyethylene.

### 8.18 Catheter lumens

There is a controversy as to whether the number of lumens in central venous catheters may impact on the incidence of CRBSI. Traditionally, multi-lumen central venous catheters have been felt to be associated with a higher risk for catheter-related infection as compared to single-lumen catheters [257,402,435,436]. Multi-lumen central venous catheters offer the benefit of simultaneous administration of incompatible drugs and may separate the administration of vasopressors and parenteral nutrition, factors which are particularly useful in the ICU.

More recently papers have questioned the contention of increased rate of infection with multi-lumen CVCs. Two recent systematic review and quantitative meta-analyses have focused on the risk of CRBSI and catheter colonisation in multi-lumen catheters compared with single-lumen catheters. The first [435] concluded that multi-lumen catheters are not a significant risk factor for increased CRBSI or local catheter colonisation compared with single-lumen devices. The second review [437] concluded that there is some evidence from five randomised controlled trials with data on 530 catheterisations - that for every 20 single-lumen catheter inserted, one CRBSI will be avoided which would have occurred had multi-lumen catheters been used. In another study involving 1396 CVCs that were prospectively studied in 1162 patients, number of lumens was noted to be an independent risk factor for CRBSI. Each additional lumen increased the risk (HR 4.4; 95% CI: 2.5-7.7; $p<0.001$) whereas the

permanent blocking of additional lumens was protective (HR 0.3; 95% CI: 0.1-0.7; p=0.006) [438].

Several guidelines advocate the use of single-lumen CVCs where feasible [1,394,395,402], with provision made for multiple ports if essential for the management of the patient. If a multi-lumen catheter is used, it is recommended that a single dedicated lumen be used for any parenteral nutrition being administered [5,20,402].

### 8.19 Catheter and venous line maintenance

The optimal time interval for routine replacement of intravenous administration sets has been studied in various well controlled trials [104,439-443]. These have been put into formalised form in recent reviews and guidelines, and are now standard practice in the multidisciplinary adult ICU at CMJAH as well as various other ICUs in South Africa and abroad [3,4,5,20]. These recommendations are shown in Table 11.

Aseptic technique is of vital importance not only during placement of CVCs but also for maintenance and when accessing the system. Catheter, tubing or syringe manipulations should be performed only after appropriate hand cleansing and optimally, the use of disposable gloves [2,3,4,5,20,21]. Hubs should be disinfected with chlorhexidine-based antiseptic solutions before accessing the extension port lumens [444]. During prolonged catheterisation, infection risk is strongly connected to the duration of catheter stay [101,337] and frequent catheter hub access increases catheter-related infection risk from colonised catheter hubs [61,194]. The number of manipulations of the central venous catheter, especially when aseptic technique is not respected, increases the risk of catheter-related bloodstream infection [5,20,21].

The continued need for the catheter should be assessed on a daily basis and removal considered when the catheter is no longer essential for medical management. A frequently arising question in catheter care and still a matter of debate, is how long a particular catheter

can be left in place if no infection is suspected [445]. Catheter replacement at scheduled time intervals remains controversial and although still practiced in some units, is not advocated in many guidelines [1,394,395]. The duration that CVCs can reasonably be left in place with adequate infection control measures has recently been addressed in a prospective randomised trial [21]. Based on the results of this study a fourteen day period in conjunction with infection control measures was felt to represent a safe time for short-term CVCs, unless removal was indicated beforehand or the catheter was no longer required [21]. This policy has now been adopted as standard practice in the multidisciplinary adult ICU at CMJAH, as well as several other centres in South Africa and some abroad.

### 8.20 Guidewire exchanges

In view of the increasing risk of CRBSI with longer catheter dwell times, scheduled guidewire exchanges of catheters have been previously proposed. However, a meta-analysis of 12 prospective randomised trials evaluating CVC replacement strategies revealed that guidewire exchanges were associated with greater risk of CRI but fewer mechanical complications than new site replacement [446]. Based on these data, guidewire exchanges should be avoided unless the risk of mechanical complications associated with the insertion of a CVC at a new site exceeds the risk of infectious complications associated with a guidewire exchange. If guidewire exchange is used, meticulous aseptic technique is necessary. The procedure should not be performed in the setting of confirmed or clinically suspected sepsis [2,3,4,5,20]. In the multidisciplinary adult ICU at CMJAH, guidewire exchanges are not practiced.

### 8.21 Catheter securement

The technique for the stabilisation of CVCs has received attention over the past decade. Suturing a CVC to the patient's skin potentially carries the risk to healthcare workers of needlestick injuries and exposure to blood-borne pathogens. In addition, evidence has

accumulated that the traditional securing of the catheter with sutures may be associated with a high risk of contamination of the exit site [402].

The use of sutureless catheter securement devices not only mitigates the risk of needlestick injury but has been recognised as an intervention to decrease the risk of phlebitis, catheter migration and dislodgement. These devices avoid disruption around the catheter entry site and may decrease the degree of microorganism colonisation and thus CRBSI [447].

### 8.22 Antimicrobial catheters

In recent years antimicrobial substances have been effectively bonded to catheters in an attempt to reduce CRI, the rationale being that impregnation or coating of the catheter polymer surface with antimicrobial agents might reduce the number of microorganisms colonising the catheter surface and thus CRBSI [2,3,4,5,20,21,101,275,337]. Antimicrobial central venous catheters are discussed in further detail in Chapter 9.

### 8.23 Heparin

There is no definite evidence that heparin reduces the incidence of CRBSI, but this may reflect a heterogeneity of heparin concentration used and its modality of administration [402]. Others have suggested that prophylactic heparin reduces the risk of thrombosis around the catheter. In view of the notion that thrombi and fibrin deposits on catheters may constitute a nidus for microbial colonisation of intravascular catheters, and thus promote infection, a meta-analysis of randomised controlled trials suggested that anticoagulant therapy may have a role in prevention [31]. Moreover these agents are also indicated in the management of patients with multiple risk factors for venous thrombosis [448-450].

### 8.24 Novel, innovative and other approaches to the prevention of catheter-related infection

A limited number of studies have reported potential innovative approaches to the prevention of foreign-body infection and CRI. Most of these address the issue of interference with biofilm

formation, a prerequisite for CRI. A suggested approach to prevent biofilm (as a prerequisite for CRI) involved the application of an external stimulus in the form of an electric field in conjunction with antibiotics. This combination was associated with an enhanced killing of biofilm embedded bacteria [451]. Related approaches aimed at eradication of biofilms include the combined use of ultrasound together with antibiotics [452,453] and extracorporeal shock waves which have been shown to have a bactericidal effect on *S. aureus* [454]. Active immunisation of rabbits with a polysaccharide [(polysaccharide-adhesin factor (PS/A)] isolated from a *S. epidermidis* strain that appears to be involved in adhesion to synthetic polymers such as silicone, led to reduced bacteraemia from catheters contaminated with the specific *S. epidermidis* strain [455].

In a further study, *S. epidermidis* prosthetic valve endocarditis was successfully prevented by active and passive immunisation of the rabbits [456]. Monoclonal antibodies against fibronectin, and other mediators of bacterial adherence to inhibit the specific adherence process, have also been proposed [457], as has the blocking of the gene operon detected in *S. epidermidis* which is responsible for autoaggregation and biofilm formation [458]. It has been shown that antibodies directed against the accumulation-associated protein (AAP) are able to prevent *S. epidermidis* biofilm formation in vitro [459]. Interference with quorum sensing, a cell-to-cell communication process which is also responsible for the regulation of biofilm formation, has also been advocated by various workers [460-462].

**TABLE 11 Replacement of intravenous tubing associated with central venous catheters** (Adapted from Mer M 2001[3], 2005[20], 2006[4], 2008 [5])

- Lines used for the administration of blood products must be replaced within 24 hours.
- Lipid-containing parenteral nutrition solutions should be completed within a 24-hour period.
- Parenteral nutrition must be administered via a single dedicated port with the administration line being replaced at 24-hour intervals (performed as a sterile procedure).
- Administration sets such as those used for the delivery of inotropes and antibiotics should be replaced at 72-hour intervals, or before if clinically indicated.
- Bridges and their attached lines, transducers and continuous flush devices can be replaced at 7-day intervals, provided there is strict adherence to aseptic technique.
- Aseptic technique also extends to care of ports and caps attached to intravascular devices and includes the spraying of a chlorhexidine-gluconate solution with manipulations.

# CHAPTER 9

# ANTIMICROBIAL CENTRAL VENOUS CATHETERS

## 9.1 Introduction

The loading of medical polymers with antimicrobial substances, either for therapeutic or preventive purposes, has a long tradition. Well known anti-infective, polymeric drug delivery systems include the polymethylmethacrylate (PMMA)-gentamicin bone cement and the PMMA-gentamicin beads (Septopal™) used for treatment of bone and soft tissue infections [463,464]. Vascular prostheses made of Dacron™ have also been treated with various antibiotic substances to create infection-resistant grafts [465-467].

In recent years, intravascular catheters or parts of the catheter system have been coated with antimicrobial agents. The main principle of such devices is that an antimicrobial substance (antibiotic, disinfectant or metal ion) is bound superficially to the catheter, either directly or by means of a carrier, or incorporated into the interior of the polymer. When such devices come into contact with an aqueous environment, the drug is released into the near vicinity. The amount of the antimicrobial substance released is influenced by the processing parameters, loading dose, applied technique, molecular size of the drug, and the physicochemical properties of the polymeric device. A high antimicrobial concentration is reached (at least initially) in the very near vicinity of the device surface, mostly exceeding the minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) of susceptible organisms. Most such materials exhibit a release pattern according to first-order kinetics, with an initially high drug release and afterwards an exponential decrease of the released drug. More sophisticated drug-release systems with defined release kinetics have also been developed.

Whether such devices are capable of inhibition of microbial adherence per se is not clear, but elimination of already adherent microorganisms should potentially be achieved for the duration that the antimicrobial compound is being released in the necessary concentrations. It is on this basis that antimicrobial substances have been deemed suitable to prevent CRI in short-term catheters which originates from contamination during the insertion or from hub colonisation [61,194,468-475].

A host of studies exist evaluating the bonding of antimicrobials to biomaterials used in the manufacture of intravascular devices. Agents involved include ampicillin, 6-aminopenicillanic acid, dicloxacillin, clindamycin, fusidic acid, teicoplanin, cefazolin, minocycline, rifampicin, cefamandole nafate and the anti-fungal miconazole (used alone or in combination) [473,474,476-482].

A range of antiseptics such as Irgasan™, iodine, benzalkonium chloride, chlorhexidine and silver sulfadiazine have also been studied [468,483,484]. Among metals with antimicrobial activity, silver has raised the interest of many investigators because of its good antimicrobial action and low toxicity. In addition there is no cross-resistance to antibiotics [465,485-488]. Further interest with silver has resulted in the development and study of devices in which the silver is distributed in the form of nanoparticles, or in combination with other elements such as carbon and platinum [489-492].

Various antimicrobial catheters are now commercially available (see Table 12). Antiseptic, antibiotic-coated and silver impregnated catheters have all been approved in the USA for patent use. The best known commercial catheters that are also in clinical use are the chlorhexidine silver sulfadiazine (CSS), minocycline-rifampin (MR) and silver in a carbon/platinum (SPC) matrix.

### 9.2 Chlorhexidine silver sulfadiazine catheters

CSS catheters have been available since the mid 1990s. A synergistic effect of chlorhexidine and sulfadiazine has been shown in vitro [493]. The catheter is polyurethane-based and impregnated with minute amounts of chlorhexidine and silver sulfadiazine. The first generation CSS catheters are coated on the external surface and according to the manufacturers, exhibit antimicrobial properties for approximately 15 days. Several million of these catheters have been sold worldwide since its introduction and a considerable number of studies and randomised clinical trials performed [99,393,494-507] and reported with this type of catheter. Most have shown a reduction in catheter colonisation. Two trials reported a significant reduction in CRBSI [99,504]. A recent meta-analysis comparing first generation CSS catheters to standard catheters reported a decreased risk of catheter colonisation and bloodstream infection [508].

In one study with longer catheter dwelling times (mean duration 20 days), no difference in the incidence of CRBSI was observed, probably reflecting less antimicrobial efficacy over time due to a loss of activity to 25% of the baseline value after 10 days in situ [500].

Second generation chlorhexidine silver sulfadiazine catheters which are impregnated on both the external and internal surfaces, have also been developed. These catheters also exhibit enhanced chlorhexidine activity. Three multicentre studies have evaluated these catheters compared to uncoated catheters in prospective randomised trials and have failed to demonstrate any effect in reducing CRBSI, although colonisation rates were lower. Such results may be related, in part, to a low baseline risk of infection as a result of the implementation of other strategies to reduce CRBSI or a lack of study power [509-511]. Development of resistance to chlorhexidine has been demonstrated in vitro among Gram-negative isolates, including *Pseudomonas stutzeri* [512]. However, in vivo resistance associated with the chlorhexidine silver sulfadiazine catheters has not been reported.

Anaphylactoid reactions, probably due to chlorhexidine, have been reported from Japan and from the United Kingdom [513].

### 9.3 Minocycline-rifampin catheters

The minocycline-rifampin catheters are coated on the inner and outer surfaces with minocycline and rifampin, which act either synergistically or additively or in combination. These catheters have been reported to be associated with a decrease in colonisation and bloodstream infection compared to standard catheters [508,514].

In a large multicentre trial comparing the MR catheter with first generation CSS catheters, it was found that the MR catheter was three-fold less likely to be colonised and 12-fold less likely to lead to CRBSI [515]. This difference has been explained by the fact that the MR catheters are coated internally and externally in contrast to the first generation CSS catheter, that the combination of minocycline and rifampicin shows better surface activity than chlorhexidine and finally, that the MR catheters retain surface antimicrobial activity longer in situ [37]. No study has compared MR catheters with second generation CSS catheters.

Although resistance against minocycline and rifampin could not be detected in clinical trials, this remains a concern as in vitro development of resistance has been demonstrated [516,517], and small increases in the minimum inhibitory concentration of MR catheters have been observed with *S. epidermidis* [517].

### 9.4 Silver, platinum and carbon catheters

Several randomised clinical trials have shown that silver, platinum and carbon catheters, which use the principle of oligodynamic iontophoresis allowing topical silver ion release, are associated with a significant decrease in catheter colonisation [490,518]. However, two prospective randomised controlled trials failed to show any benefit of these catheters in reducing catheter colonisation and CRBSI [392,519]. A multicentre randomised study evaluated

catheters impregnated with ionic silver in 577 ICU patients and 627 CVCs. Compared to standard catheters, impregnated catheters had no effect on colonisation or bloodstream infection prevention [520].

A meta-analysis evaluating the pooled results from available trials indicated that silver alloy coated, silver-impregnated and silver-iontophoretic CVCs (SPC-CVC) did not reduce catheter tip colonisation or CRBSI. These types of catheters were also reported to be inferior to first-generation CSS and MR CVCs. The same analysis concluded that both the first-generation CSS CVCs and MR CVCs significantly reduce catheter tip colonisation and CRBSI, compared to uncoated catheters [521].

### 9.5 Cost-effectiveness

The cost-effectiveness of antimicrobial catheters has also been advocated. Despite the additional acquisition cost, the use of such catheters has been reported to potentially decrease hospital costs [99,522,523,524].

### 9.6 Guidelines

The USA guidelines suggest that antimicrobial and anti-infective catheters be considered for use in adults with an expected catheter duration time of greater than five days in settings where CRBSI rates are high [1,396]. The UK guideline recommends considering the use of an antimicrobial impregnated central venous catheter for adult patients who require short-term (less than 10 days) central venous catheterisation and who are at high risk for CRBSI [395]. In the German guideline [394] the use of antimicrobial catheters is regarded as a controversial issue and is still a matter of debate. No recommendations are given for the use of these catheters in paediatric patients in any of the three guidelines.

**TABLE 12 Examples of commercially available antimicrobial intravascular catheters**

| Catheter Trade Name | Manufacturer | Principle |
|---|---|---|
| ArrowGard [a]<br>ArrowGard Plus [b] | Arrow International, USA | Chlorhexidine +<br>Silversulfadiazine |
| Cook Spectrum | Cook Critical Care, USA | Minocycline + Rifampin |
| AMC Thromboshield | Baxter, USA | Benzalkoniumchloride-Heparin |
| Vantex Oligon | Edwards Life Sciences, USA | Silver, Carbon, Platinum |
| Logicath AgTive | Smiths, UK | Silver nano-sized particles |

[a] Only externally coated
[b] Impregnated on external and internal surfaces

## CHAPTER 10

## GUIDELINES

Over the past decade various international guidelines have been published. These include the United States (US) Guideline for the prevention and control of intravascular catheter-related infections [1] which replaced the former guideline [525], the German guideline provided by the Commission for Hospital Hygiene and Infection Control at the Robert Koch Institut (RKI) [394] and the United Kingdom (UK) guidelines [395].

The US guideline [1] was intended to provide evidence-based recommendations for the prevention of CRI and to address medical personnel involved in catheter insertion and catheter care, as well as persons responsible for surveillance and control of infections in health care facilities. The guideline was prepared by a group of expert professionals from various fields including critical care, infectious diseases, health-care infection control, surgery, anaesthesiology, interventional radiology, pulmonary medicine, nutrition, oncology, paediatrics and nursing. Categorised recommendations are given to inform the user on the strength of the respective recommendations.

The German guideline [394] is evidence-based and also uses categorised recommendations. A separate chapter is provided for each different catheter type and for infusion therapy in general.

The UK guideline is part of the general guidelines for preventing hospital-acquired infections [395]. The evidence of the recommendations is graded with all the recommendations endorsed equally and none regarded as optional. They are divided into seven distinct interventions which include selection of catheter type and insertion site, aseptic technique during catheter insertion, cutaneous antisepsis, catheter and catheter site care, catheter replacement strategies and antibiotic prophylaxis.

A comparison of these national guidelines is summarised in Table 13.

Guidelines for the management and prevention of nosocomial infections in South Africa, including intravascular infections, have also been published [20,82,83]. Most recently, an update on intravascular catheter infection prevention guidelines has been published by the Centers for Disease Control and Prevention (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) [396,526].

A summary of specific recommendations from the CDC and HICPAC is included in Table 14.

**TABLE 13 Selected recommendations for the prevention catheter-related infections: comparison of three national guidelines** [395,1,394]

| Preventive measure | USA | UK | Germany |
|---|---|---|---|
| **Catheter insertion:** | | | |
| Education of medical personnel | Yes | - | Yes |
| Catheter type and material | | | |
| Preferential use of single lumen catheters | Yes | Yes | Yes |
| Preference of PUR and Teflon catheters | - | - | Yes |
| Use of antimicrobial catheters in high-risk adult population when other preventive measures have not decreased infection rates | Yes | Yes | Unresolved Issue |
| **Catheter insertion site:** | | | |
| Choice of subclavian rather than jugular or femoral vein for CVCs | Yes | Yes | Yes |
| Preparation of insertion site with chlorhexidine-containing antiseptics | Yes | Yes | No preference of chlorhexidine |
| **Use of maximum sterile barriers during insertion of CVCs** | Yes | Yes | Yes |
| **Use of specially educated personnel (IV team)** | Yes | - | - |
| **Antimicrobial prophylaxis** | No | No | No |
| **Catheter care:** | | | |
| Catheter site dressings | | | |
| Exchange of damp, dirty, or loosened dressings | Yes | Yes | Yes |
| Use of either gauze or transparent dressings | Yes | Yes | Yes |
| Use of topical antimicrobials | No | No | No |
| Replacement of catheters and administration sets | | | |
| Exchange of peripheral IV catheters every 72-96 h | Yes | - | No routine exchange |
| Removal of a catheter no longer needed | Yes | Yes | Yes |
| Exchange of administration sets every 72 h | Yes | Yes | Yes |
| Exchange of administration sets within 24h if lipids or blood (products) are administered | Yes | Yes | Infusion time for lipids 12 h, blood 6 h |
| Use of in-line filters | No | - | No |
| Surveillance | | | |
| Daily inspection of catheter site | Yes | - | Yes |
| Recording of operator, date, and time of catheter insertion, dressing changes and removal | Yes | - | - |
| Documentation of infection rates of CRBSI according to a standardised protocol with accepted definitions for CRI following inter-hospital comparison | Yes | - | - |

**TABLE 14: Guidelines for the prevention of intravascular catheter-related infections, 2011** [396]

| Summary of specific updated recommendations |
|---|
| . Healthcare personnel should be educated regarding the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters, and appropriate infection control measures to prevent intravascular catheter-related infections. Knowledge of and adherence to these guidelines should be assessed periodically for all personnel (Category IA).<br>. Appropriate nursing staff levels in intensive care units should be ensured (Category IB).<br>. Catheters should be selected based on the intended purpose and duration of use, known infectious and non-infectious complications, and experience of individual catheter operators (Category IB).<br>. For CVCs, a subclavian site, rather than a jugular or a femoral site, should be used in adult patients to minimise infection risk for non-tunnelled CVC placement (Category IB).<br>. Ultrasound guidance should be used to place CVCs (if available) to reduce the number of cannulation attempts and mechanical complications (Category IB).<br>. A CVC should be used with the minimal number of ports or lumens essential for treatment of the patient (Category IB).<br>. When adherence to aseptic techniques cannot be ensured, the catheter should be replaced as soon as possible, i.e. within 48 hours (Category IB).<br>. Maximal sterile barrier precautions, including the use of a cap, mask, sterile gown, sterile gloves, and a sterile full body drape, should be used for the insertion of CVCs, PICCS, or guidewire exchange (Category IB).<br>. Skin preparation entails preparing clean skin with a ≥ 0.5% chlorhexidine preparation with alcohol before CVC insertion. If there is a contraindication to chlorhexidine, tincture of iodine or 70% alcohol can be used as alternatives (Category IA).<br>. A chlorhexidine/silver sulfadiazine or minocycline/rifampicin-impregnated CVC should be considered in patients whose catheter is expected to remain in place for more than 5 days where CRBSI rates are high (Category 1A).<br>. Systemic antimicrobial prophylaxis should not be administered routinely before insertion or during use of an intravascular catheter to prevent catheter colonisation or CRBSI (Category IB).<br>. Anticoagulant therapy should not be used routinely to reduce the risk for catheter-related infection in general patient populations (Category II).<br>. Hospital-specific or collaborative-based performance improvement initiatives in which multifaceted strategies are “bundled” together to improve compliance with evidence-based recommended practices should be used (Category IB). |

Category IA: Strongly recommended for implementation and strongly supported by well-designed experimental, clinical and epidemiological studies

Category IB: Strongly recommended for implementation and strongly supported by some experimental clinical and epidemiology studies, and a strong theoretical rationale

Category II: Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale

## CHAPTER 11

## PRINCIPLES OF TREATMENT OF CATHETER-RELATED INFECTION

Treatment depends on the stage of infection and the pathogen [2,3,4,5,20]. As a general rule, when CRBSI is suspected, the common practice in the ICU is to remove the CVC and replace it at a new site if ongoing use of a CVC is required [2,3,4,5,20,60].

As many catheters may be removed unnecessarily, some authors/workers have suggested a more conservative approach of "watchful waiting" with appropriate investigations being performed and ongoing clinical evaluation [60,527].

Figure 4 summarises the current approach to the management of patients with short-term central venous catheter-related bloodstream infection.

### 11.1 Catheter removal and rationale

Although some authorities have suggested that it may be acceptable to retain the catheter in situ and treat with appropriate antimicrobial therapy when the CRBSI is caused by coagulase-negative staphylococci, failure to remove the CVC is associated with a substantial chance of recurrence [2,3,4,5,20,60]. Three observational prospective studies have shown that removal of the CVC in the setting of *S. aureus* CRBSI, including uncomplicated cases, is associated with a more rapid response to therapy and a lower relapse rate [178,528,529]. In the setting of uncomplicated *S. aureus* CRBSI, the catheter should be removed and at least 2 weeks of parenteral antibiotics given. There is a high relapse rate if these are given for a shorter time [2,3,4,5,20,179,529].

Failure to remove the catheter with CRBSIs due to Gram-negative bacilli such as *Klebsiella pneumoniae, Enterobacter species, Pseudomonas species, Acinetobacter species* and *Stenotrophomonas maltophilia*, has been reported to be associated with a higher rate of treatment failure, relapse and bacteraemic recurrence [530]. In view of this, it has been

suggested that Gram-negative bacillary CRBSI should be managed with removal of the CVC in conjunction with an appropriate course of antibiotics [530,531].

At least five prospective studies have shown that CVC removal is associated with improved outcome in patients with candidaemia [532]. These include large prospective studies in which catheter retention proved to be a significant factor for the persistence of candidaemia, or was associated with higher mortality. In a study prospectively analysing the risk factors for death in 145 patients with nosocomial candidaemia, catheter retention was found to be an independent variable for increased risk of death in multivariate analysis, independent of persistent neutropenia [242]. Recent controversial but challenging data in candidaemia evaluating patients treated with echinocandins or liposomal Amphotericin B, which have biofilm penetrating properties, has suggested CVCs could possibly remain in situ if these agents were used in this setting [240]. This approach is currently neither a widely accepted policy, nor is it practice at the multidisciplinary ICU at Charlotte Maxeke Johannesburg Academic Hospital. Retention of an infected catheter has most recently been shown in a meta-analysis involving seven randomised trials and 1915 patients in the setting of invasive candidiasis, to be associated with increased mortality [137].

In cases of septic shock or severe sepsis of undetermined origin, or when frank local signs of infection are found, the catheter should always be removed [60,305,309,402].

When conservative strategies have been adopted, the decision for catheter removal depends on the microorganisms and on the evolution of the patient's state during the first 48 hours. If blood cultures recover *S. aureus, enterococci*, gram-negative bacilli or fungi, the catheter should be removed [60,275,305]. Overall, conservative strategies are deemed to be risky in critically ill patients [60]. When such an approach is embarked upon patients must be continuously monitored.

**11.2 Antimicrobials** (see Figure 4)

When a CRBSI is associated with severe sepsis or shock, antimicrobial therapy should be administered timeously together with catheter replacement [305]. Broad spectrum antimicrobial cover is normally advised and should be based on local epidemiology as well as antimicrobial susceptibility patterns. This treatment should then be de-escalated according to the results of catheter tip cultures and blood cultures [305].

In cases of CRBSI, the duration of treatment should be at least 14 days for uncomplicated *S. aureus* and *Candida* species [305]. For CRBSI-associated with *Pseudomonas* species and *Acinetobacter* species, a similar duration of time should be considered [305]. For other microorganisms and with uncomplicated catheter-related infection, antimicrobial therapy should not exceed 7 days if the catheter has been removed. Uncomplicated CRBSI refers to regression of septic signs and bacteraemia within 3 days and no persistent infectious site. *Staphylococcus lugdunesis* should be treated in a similar fashion to *S. aureus* [305].

Vancomycin is generally recommended for empirical therapy in health care settings with an elevated prevalence of MRSA. For institutions in which the preponderance of MRSA isolates have Vancomycin minimum inhibitory concentrations (MIC) values ≥1.5μg/ml (and probably ≥1μg/ml), alternative agents such as daptomycin are advocated [395,533]. Linezolid administration is not advocated for empirical therapy (ie. patients suspected but not proven to have CRBSI) [305]. Empiric coverage for Gram-negative bacilli should be based on local antimicrobial susceptibility data and the severity of the disease. Examples of agents include fourth-generation cephalosporins, carbapenems, or β-lactam / β-lactamase combinations, with or without an aminoglycoside [305].

For empirical treatment of suspected catheter-related candidaemia, use of an echinocandin, or in selected patients fluconazole, is recommended. Fluconazole could be considered for patients without recent azole exposure and in health care settings where the risk of *Candida*

*krusei* or *Candida glabrata* infection is very low [305]. Systemic antifungal therapy (together with removal of the catheter) should be given in all cases of catheter-related candidaemia in view of the potentially significant sequelae [2,3,4,5,20,534]. Deoxychelate-Amphotericin B has previously been used in this setting [3,4,5,20,535]. Newer agents are, however, felt to be less toxic. Agents such as Voriconazole which covers *Candida albicans* as well as non-albicans species, and lipid formulations of Amphotericin B have also been used in this setting [4,5]. Initiation of empirical therapy for suspected catheter-related candidaemia is recommended for septic patients who are already on broad-spectrum antibiotics, where there is no evidence of overt sepsis elsewhere, and with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, haematologic malignancy, receipt of bone marrow or solid-organ transplant, and femoral catheterisation or colonisation due to *Candida* species at multiple sites [60,305,309].

Empiric combination antibiotic coverage for multi-drug-resistant (MDR) Gram-negative bacilli, such as *Pseudomonas aeruginosa* is suggested when CRBSI is suspected in neutropenic patients, severely ill patients with sepsis, or patients known to be colonised with such pathogens until the culture and susceptibility data are available and the antibiotic regimen can be de-escalated [305,309].

### 11.3 Other approaches

Some workers have suggested that although antimicrobial therapy is frequently administered and advocated, many of the infectious complications may be self-limited and resolve after removal of the catheter. This may be applicable to cases associated with CoNS and *Enterobacteriaceae* [2,3,4,5,20,60]. Antimicrobials should, however, be administered if there is persistent sepsis despite catheter removal in immunosuppressed patients, or if there is evidence of complications [2,3,4,5,20,60].

### 11.4 Catheter salvage therapy

In some rare circumstances, catheter salvage therapy has been advocated in the ICU [305,309] with the use of antibiotic lock therapy. This treatment should only be considered in the absence of severe sepsis and when *Candida* species, and *S. aureus* (and probably *Pseudomonas* species and *Acinetobacter baumannii*) are not the responsible organisms [60]. An additional drawback in the ICU is that the catheter needs to be unused during the antibiotic lock process, thus further limiting the potential usefulness. For patients with CRBSI in whom catheter salvage is attempted, blood cultures should be obtained, and the catheter should be removed if 2 sets of blood cultures on a given day (one set is acceptable in neonates) remain positive for microorganisms when drawn 72 hours after initiation of appropriate therapy [305,309].

### 11.5 Complications

Complications of CRBSI include septic thrombosis of the great veins [532,536], endocarditis and metastatic foci of infection [2,3,4,5,20,536].

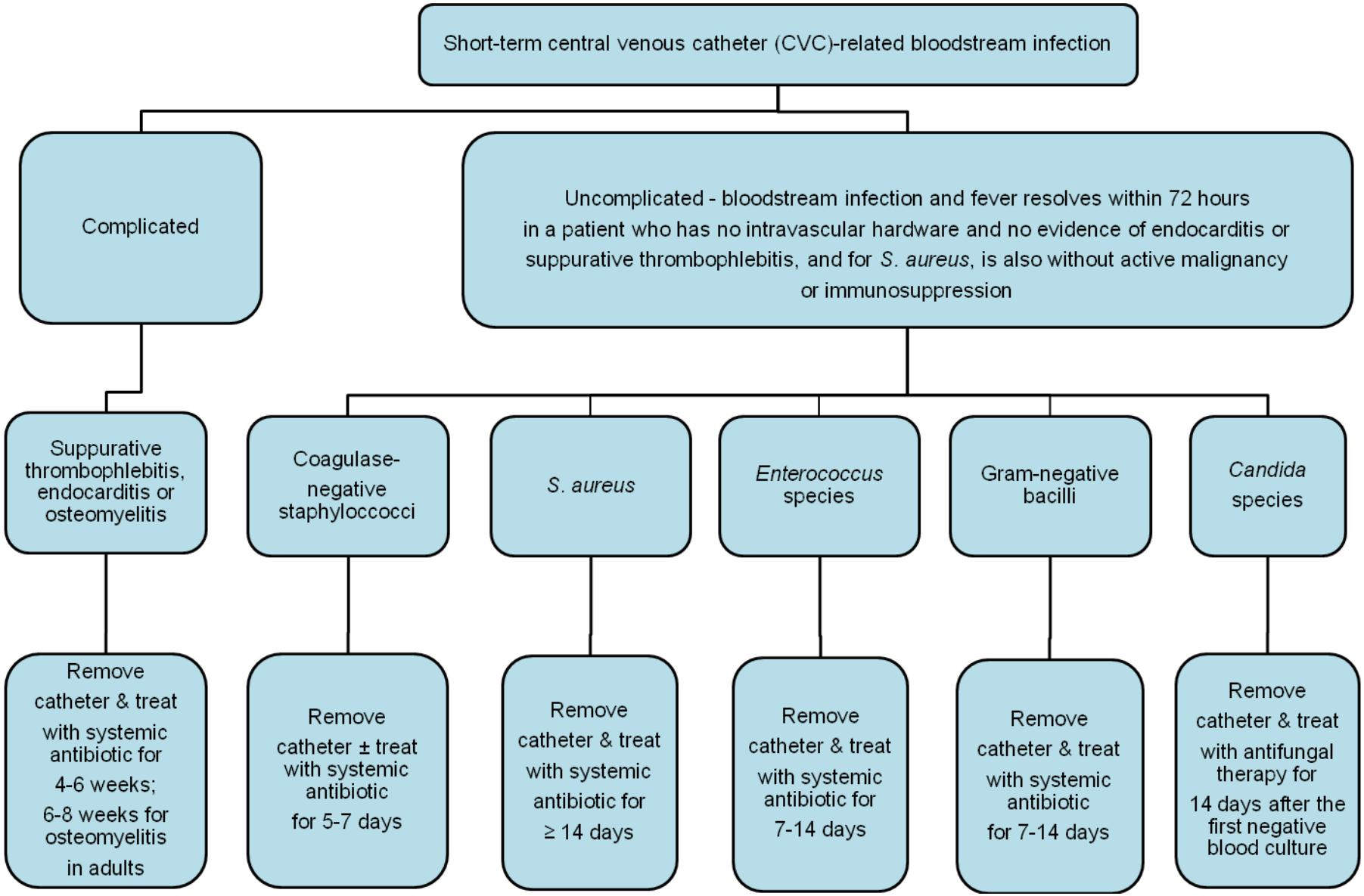
The strongest predictor of complicated *S. aureus* bacteraemia is the persistence of fever and/or bacteraemia for more than 72 hours after catheter removal and initiation of antibiotics [179,537]. In patients with *S. aureus* CRBSI and persistant fever or bacteraemia, transoesophageal echocardiography should be performed to rule out infective endocarditis [305,309,325,537].

Four to 6 weeks of antibiotic therapy is advocated in patients with persistent fungaemia or bacteraemia after catheter removal (ie. occurring beyond 72 hours after line removal), in patients who are found to have infective endocarditis, suppurative thrombophlebitis, and in paediatric patients with osteomyelitis. Six to 8 weeks of therapy should be used for the treatment of osteomyelitis in adults [305,309].

### 11.6 Special situations

For CRBSI due to less virulent microbes that are difficult to eradicate such as *Bacillus* species, *Micrococcus* species or *Propionibacterium,* catheters should generally be removed after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least one blood culture sample drawn from a peripheral vein [305].

**Figure 4: Approach to the management of patients with short-term central venous catheter-related bloodstream infection**



## CHAPTER 12

## STUDY PROTOCOL

### 12.1 Aims of this study

The aims of this study were to determine whether the duration of central venous catheter insertion time could safely be increased from the standard practice of seven days in the adult multidisciplinary ICU at CMJAH, to fourteen days, to assess the influence of an antimicrobial impregnated catheter on the incidence of CRI, as well as to elucidate the epidemiology and various risks of CRI in a population of critically ill patients, including clinically evident catheter-related thrombosis.

### 12.2 Materials and methods

This was a prospective, randomised, double-blind study performed in the adult multidisciplinary intensive care unit at CMJAH, South Africa over a four year period. The study included 118 critically ill medical, surgical, trauma and obstetric/gynaecological patients, and entailed comparison of a 14 day placement of standard triple lumen (ARROW Standard Triple Lumen Catheter, Arrow International Inc., Reading, Pa, US) versus antimicrobial impregnated (CSS; ARROWgard$^{TM}$ Triple Lumen Catheter, Arrow International Inc., Reading, PA, US) CVCs on the rate of CRI.

The two types of catheters were of identical appearance and were subsequently differentiated by a numerical code which was broken only on completion of the study.

The randomisation protocol involved equal numbers of the two types of non-distinguishable catheters being mixed in consignments and then selected in a consecutive fashion for placement in study candidates.

Exclusion criteria for the study were age less than 18 years, white blood cell count on admission of less than $4x10^9$/L, skin burns and a history of allergy to sulpha-containing preparations. No guidewire exchanges were performed.

Standard infection control measures were practiced with catheter insertion. This included handwashing, the use of sterile gowns, sterile gloves, full sterile drapes, masks and caps. The catheters were placed by the ICU medical staff, including intensivists, fellows and registrars in training, into the right or left subclavian or internal jugular veins as judged most appropriate by clinical evaluation.

Skin swabs were taken for culture prior to cleansing and catheter insertion. The skin insertion site was cleansed with a 0.5% chlorhexidine-gluconate in 70% alcohol solution. Catheters were inspected and dressed daily and a clinical assessment undertaken for any evidence of catheter-related thrombosis. The catheters were studied for colonisation and CRBSI at removal. The origin of each CRBSI was sought by culturing all potential sources (skin, catheter segments, hubs and infusate). A semi-quantitative culture was performed on the catheters using the roll-plate technique as described by Maki et al.[100]. DNA-molecular typing was employed to assist in microbiological analyses. All relevant clinical data was collected and evaluated.

CRI was defined according to the criteria proposed by the Centers for Disease Control and Prevention [96]. Definitions used for identifying the source of an isolate causing a CRBSI are shown in Table 15.

Catheters remained in place until they were no longer required, a specific event necessitated removal, or for 14 days, whichever occurred first. All existing intravascular catheters were removed prior to insertion of the study catheters.

Any parenteral nutrition administered was delivered via a single dedicated port.

## 12.3 Collection and processing of specimens

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

Ten square centimeters of skin about the catheter site was sampled. A sterile template was applied to the site and the exposed area cultured with a 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 in a direction perpendicular to the first. 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 plates (done in triplicate) and incubated aerobically at $35^0$C overnight. All colony types were enumerated using routine laboratory methods.

### 12.3.2 Collection and processing of specimens from catheter hubs

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

### 12.3.3 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 in the laboratory, the infusate was centrifuged and the deposit cultured onto a segment of a blood agar plate (incubated at $35^0$C for 72 hours) and in 10 ml of brain heart infusion

broth and incubated at $35^0$C for 7 days, before being terminally sub-cultured and discarded.

### 12.3.4 Collection and processing of blood cultures

In the setting of local or systemic sepsis, a set of blood cultures was obtained both percutaneously from a single venepuncture site, as well as through the catheter (patients with fever, other sites of infection, or inflammation of the insertion site). In the absence of local or systemic sepsis, a set of blood cultures was routinely taken from 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. Clinicians were advised to collect no less than 5 ml of blood in each Bactec® bottle. Blood cultures were processed at $35^0$C for 7 days by the BACTEC-460® radiometric method. Fungal blood cultures were processed using conventional methods.

### 12.3.5 Collection and processing of catheter segments for culture

To prevent contamination by skin organisms, the skin around the insertion site was cleansed with 0.5% chlorhexidine gluconate in 70% alcohol and allowed to dry prior to removal. Catheters were removed aseptically keeping the externalised portion directed upward and away from the skin surface to minimise contamination by skin organisms. The distal intravascular tip and the proximal transcutaneous segments of the catheter were submitted to the laboratory for bacteriological processing after being cut with a sterile scapel into 5 cm portions. The two segments of the catheter were sent to the laboratory in sterile universal containers and cultured within 2 hours of collection to prevent dessication of micro-organisms. A semi-quantitative culture was performed on the catheters using the method described by Maki [100] with colony types subsequently enumerated and micro-organisms identified.

### 12.4 Statistics

Statistical analysis was performed using logistic regression, the Wilcoxan Mann-Whitney test and a chi-squared contingency table test [538-541].

A chi-squared contingency table test was used when testing for differences between the catheter types versus categorical variables such as sex, and yes/no variables such as site, systemic sepsis, parenteral nutrition, ventilation and reason for admission.

Where the test was between the catheter types and continuous variables such as age and number of bacteria around the insertion site (either prior to insertion or at the time of removal), a Wilcoxon-Mann-Whitney test was used.

The reason for use of a nonparametric test rather than a t-test or an Analysis of Variance is that the data used cannot be assumed to be from a normal distribution, i.e. the data are skewed. This is also the reason why the median and range of the ages was reported (median 47, range 18-83)

In order to investigate possible confounding due to covariates, logistic regression was used. This allowed testing for a difference between the catheter types once a covariate or multiple covariates is/are taken into account.

A p-value less than 0.05 was considered significant.

### 12.5 Ethics Approval and International Protocol Registration

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand (M941129) and the protocol registered with ClinicalTrials.gov protocol registration system (NCT00533988). Informed consent was obtained for all participants.

## CHAPTER 13

## RESULTS

Sixty two patients received a standard triple-lumen catheter and 56 patients a CSS impregnated triple-lumen catheter. The study spanned 34,951.5 catheter hours (≡1,456 catheter days, ≡3.99 catheter years).

Patient demographics and risk factors for CRI were similar in both groups (see Table 16). However, significantly more trauma patients received a standard catheter [20/62 (32%) vs. 9/56 (16%)] p=0.0449. There was no significant difference in infections between the catheters, after taking trauma into account (p=0.8464).

Following catheter insertion, bloodstream infection was diagnosed in 18 patients, one of whom died. Primary CRBSI occurred in 15 patients and in three cases the CVC was contaminated following haematogenous seeding. Five patients demonstrated catheter colonisation. Ninety-five catheters (81%) (49 standard, 46 CSS) had neither evidence of colonisation nor bloodstream infection. The mean duration of placement of these 95 CVCs was 12.4 days.

Thirty-three catheters (17 standard, 16 CSS) were removed prior to 14 days (suspected sepsis, accidental displacement, death, no longer required).

Of the CVCs left in place for 14 days, 84% had no evidence of catheter colonisation or bloodstream infection (71/85). The mean duration of placement for the full sample of 118 CVCs was 12.3 days (range 1 – 14). No statistically significant differences between the two catheters could be demonstrated in terms of number of days of catheter placement (p=0.3341) and colonisation or bloodstream infection (13/62 vs. 10/56) vs. no infection (p=0.6704) (see Table 16).

Furthermore, no statistically significant difference in CRBSI or colonisation between the two catheters could be demonstrated for removal at or before 7 days (p=0.6003) and after 7 days (p=1.000).

The site of CVC insertion (internal jugular vein versus subclavian vein), the administration of parenteral nutrition and bloodstream infection at the time of catheter insertion were not noted to be risk factors for catheter infection (p=0.1617, 0.5449 and 0.4575). In addition, no statistical difference could be demonstrated between the two catheters for these variables (p=0.3320, 0.5868 and 0.1861). A significantly greater number of patients had an internal jugular vein insertion site (95 vs. 23; p<0.0001).

The most common source of primary CRBSI was skin, followed by hub and infusate. There was no statistical difference between the two catheters.

The most common microorganism isolated as a cause of CRBSI was CoNS. Other microorganisms associated with CRBSI included *S. aureus* and various gram-negatives such as *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Acinetobacter baumanii*, *Providencia* species and *Alkaligenes faecalis*. A yeast was identified in one case (CSS catheter). Primary CRBSI occurred in nine cases with a standard catheter and in six cases with a CSS catheter. There were no significant differences between the catheters in terms of the nature of the micro-organisms causing CRBSI.

Similarly, with respect to colonisation, there were no significant differences in the nature of the colonising bacteria between the two catheters. CoNS were the most commonly isolated coloniser involving three catheters (two standard catheters, one CSS), with *Enterobacter cloacae* (standard CVC) and *Bacillus cereus* (CSS CVC) being the other two colonisers.

No statistically significant differences were noted in the number of bacteria colonising the skin around the CVC insertion site both prior to catheter insertion and at the time of catheter

removal on analysis of colony forming units of isolates (p=0.08). CoNS constituted the majority of 161 skin colonisers that were isolated (60%). Other bacteria isolated from the skin cultures in descending order of frequency included Enterobacteriaceae (10%), *Bacillus* species (7.5%), *Acinetobacter baumanii* (5%), *S. aureus* (4%), enterococci (4%), diptherioids (4%), *Pseudomonas* species (3%) and *Streptococcus* species (2.5%). For each of these microorganisms, there were no statistically significant differences between isolates when comparing the two types of catheter (p> 0.05).

No significant non-infectious complications such as pneumothorax related to catheter placement were documented. There was no clinical evidence of catheter-related thrombosis in either of the study groups.

**TABLE 15**

**Definitions for identifying the source of a catheter-related bloodstream infection**

**Infusate-related infection:** same organism present in the infusate, central venous catheter hubs and central venous catheter distal segment. Skin cultures negative.

**Hub-related infection:** same organism recovered from the central venous catheter hub, the central venous catheter distal segment and blood cultures. Cultures of infusates negative. Skin cultures negative, or positive for different cultures.

**Skin-related infection:** same microorganism isolated from the skin, the central venous catheter transcutaneous segment, the central venous catheter distal segment and blood cultures.

**Hematogenous seeding of the central venous catheter:** same microorganism isolated from blood cultures, the central venous catheter distal segment and a distant source of infection. Cultures of infusate/s, central venous catheter hubs and skin negative.

**TABLE 16 Characteristics of 118 critically ill patients enrolled in the study**

| Patient demographics | Standard catheter | CSS catheter |
|---|---|---|
| Number of patients | 62 | 56 |
| Median age in years (range) | 47 (18 – 83) | 43 (18 – 78) |
| Sex M:F | 38 : 24<br>(61%) : (39%) | 34 : 22<br>(61%) : (39%) |
| Systemic sepsis at time of CVC insertion | 36 (58%) | 33 (59%) |
| Parenteral nutrition | 33 (53%) | 27 (48%) |
| Ventilation | 54 (87%) | 55 (98%) |

CSS = Chlorhexidine silver sulfadiazine
CVC = Central venous catheter

**TABLE 17 Colonisation and infection data comparing standard catheter vs CSS catheter**

| Colonisation / Infection | Standard catheter | CSS catheter | P value |
|---|---|---|---|
| Colonisation | 3 | 2 | NS |
| Infection | 10 * | 8 # | NS |
| Colonisation and infection | 13 * | 10 # | NS |
| None | 49 | 46 | NS |
| Total | 62 | 56 | |

***** = Includes one case of hematogenous seeding of the catheter

**#** = Includes two cases of hematogenous seeding of the catheter

NS = Non-significant

CSS = Chlorhexidine silver sulfadiazine

CVC = Central venous catheter

## CHAPTER 14

## DISCUSSION

This study examined the influence of antimicrobial impregnated central venous catheters on the incidence of catheter-related infection, whether CVCs can safely be left in place for a period of up to 14 days, as well as elucidating the epidemiology and risks (such as insertion site, clinical evidence of thrombosis and the use of parenteral nutrition) of catheter-related infection in a population of critically ill patients.

Exactly how long non-cuffed short term CVCs can safely be left in place, particularly in critically ill patients, has not been previously assessed [33,34]. In general, most studies that have evaluated duration of placement as a risk factor have shown that prolonged placement significantly increases the cumulative risk of infection, particularly if longer than 5 - 7 days [26,256,436,542,543,]. Indeed, a critical review of well designed published studies of risk factors for CVC-related bloodstream infections revealed that duration beyond 7 days was associated with a significantly increased risk of CRBSI [33]. Despite suggestions that routine replacement of CVCs at short term intervals such as every 4 - 5 or 7 days may not significantly reduce the risk of CVC-related BSI in patients requiring prolonged central access, this has not been conclusively established [30]. While some studies report no decline in the incidence with routine replacement, most have not had sufficient statistical power to answer this question [33]. Because the issue of “safe” duration of catheter retention has remained controversial and unanswered [33], scheduled replacement remains widely practiced in many ICUs, despite currently available guidelines and recommendations. In a study in mainland Britain where 165 ICUs were surveyed, catheters were routinely replaced in the majority, the mean time being 6.5 days [544].

It is felt that this study with almost 35,000 hours of catheter dwell time provides an ample basis to advocate “safe” CVC dwell time and offers suitable direction. The need for an intravascular

catheter should however, be frequently assessed and the device should be removed as soon as the intended use is over [21,545].

Over the past several years, antimicrobial impregnated CVCs have been introduced in an attempt to limit catheter-related infection and increase the time that CVCs can safely be left in situ. Several studies and meta-analyses have reported the benefit of these CVCs in the prevention or reduction of CRI [36,37,39,99,393,494-498,500-507,515]. Cost efficacy has also been claimed [99,522-524,546].

On the basis of this data, various advisory panels and authorities have recommended the use of antimicrobial impregnated CVCs in selected clinical settings [1,39,40,59,395,396,542,547-549]. However, their role remains controversial with various workers suggesting that more work is required to support or refute the hypothesis that they may reduce the rate of, or prevent CRBSI [38,550].

A recent review of eleven randomised studies failed to demonstrate any significant clinical benefit associated with the use of antimicrobial impregnated CVCs for the purpose of reducing CRBSI or improving patient outcome [550]. Concern about the emergence of antimicrobial resistance with long term use of these catheters has also been expressed [38,517,547,548,550-552].

This study was unable to demonstrate any benefit of an antimicrobial impregnated catheter (CSS) over standard catheters in critically ill patients. Of interest, there was no difference in colonisation or bloodstream infection rate between the two catheters prior to or after 7 days, which appears to refute the contention that antimicrobial impregnated catheters may be of particular value. Furthermore, a significantly greater number of trauma patients received a standard catheter, a variable recognised to potentially increase the rate of CRI.

Placement of CVCs in the internal jugular or femoral vein rather than the subclavian vein has been associated with a significantly increased risk of CRBSI [33,388,389,390,391]. The subclavian vein is currently recommended as the preferred site of placement of CVCs in several guidelines and reviews [33,39,396,553]. Several studies, including one randomised clinical trial, have found that percutaneous placement of a CVC in an internal jugular or femoral vein is associated with a substantially higher risk of CRSBI than subclavian vein placement [25,33,97,554-556]. It has been postulated that internal jugular vein placement may be associated with greater rates of CRI due to possible contamination from oro-nasal and airway secretions, a higher incidence of CVC-related thrombosis, as well as difficulty in adequately securing the catheter.

In this study, we were unable to demonstrate any difference in catheter infection related to site of CVC insertion when comparing internal jugular vein versus subclavian vein placement. This was despite the fact that a significantly greater number of patients had an internal jugular vein insertion site. There was also no statistical difference when comparing the standard versus CCS impregnated catheters.

Similarly, the use of parenteral nutrition has also been well documented to be a risk factor for CRBSI with non-cuffed percutaneously inserted CVCs [33,557]. In this study, the administration of parenteral nutrition via a single dedicated port was not noted to be a risk factor for catheter infection and again, there was no statistical difference between the two types of catheters.

Patients with CVCs in situ have previously been reported to be at high risk for catheter-related thrombosis, especially if the catheter has been in place for one week or more [29,30,558]. Of particular relevance, is that the risk of CRI has been strongly correlated to the presence of catheter-related thrombi [29,30,31,32]. The risk of catheter-related thrombosis appears to be greatest with femoral venous catheters, followed by those placed in the internal jugular vein, with the least risk reported to involve subclavian venous catheters [140,156,559]. The risk of

thrombosis is documented to be four-fold greater with internal jugular lines as compared to subclavian vein catheters [156]. Recognised predisposing factors to venous thrombosis include catheter-related factors (indwelling time, diameter, CVC material), procedural factors (difficult or traumatic insertion) and patient factors (insertion site, blood viscosity, activation of coagulation factors due to the underlying disease) [32,559].

In this study, there was no clinical evidence of catheter-related thrombosis in any of the patients, despite the majority of the patients having an internal jugular vein insertion site, a minimum of one of the predisposing factors, and a mean dwell time well beyond one week. The administration of subcutaneous low-molecular-weight heparin as part of the routine management of these patients may have decreased the risk of clinically apparent thrombus formation.

Experience with insertion technique has been identified as an important risk for CVC-related BSI [33,331]. Studies have shown that intensified training and educational programs can substantially reduce the baseline risk of CRBSI [560,561]. This study was performed in an academic training unit with a large turnover of junior staff, many of whom were involved in catheter placement. This in conjunction with the background severity of illness of the patients involved may have been contributing factors to the documented CRIs. All the patients in this study had at least one major organ failure and were initially assessed to be likely to spend a substantial amount of time in ICU and hospital and thus be potential candidates for 14 day catheter dwell time.

Subsequent to this study a dedicated policy regarding the insertion, maintenance and use of CVCs has been developed. The basic principle revolves around strict adherence to aseptic technique at all times and has been described in recent reviews [3,4,20]. It is currently the unit policy in the multidisciplinary adult ICU at CMJAH to leave standard CVCs in situ for up to 14 days in critically ill patients after which time the device is replaced and resited if it is deemed

necessary. Since the introduction of this practice and with ongoing repetitive education it is now the exception that a CVC is removed for suspected CRI.

Epidemiologically, the most common source of primary CRBSI was skin followed by hub and infusate. No difference could be demonstrated between the two catheters. These findings are similar to those previously reported.

## CHAPTER 15

## CONCLUSION

In this study, no significant difference in CRI rates between standard and CSS impregnated CVCs could be demonstrated. Standard CVCs can safely be left in situ in critically ill patients for up to 12 days and probably 14 days, with appropriate infection control measures. The most common source of CRI was the skin. Administration of parenteral nutrition and the site of catheter insertion (subclavian vein versus internal jugular vein), were not noted to be risk factors for CRI. Furthermore, there was no clinical evidence of catheter-related thrombosis in any of the patients.

The data and observations presented in this study are important and offer direction for the use of CVCs in critically ill patients, irrespective of location, particularly in light of the many controversies that exist, and also in view of the suggestions by various workers in the field that more data on the subject is required and that there is room for improvement in central venous catheter care [562,563].

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**STUDY PAPER** (see appendix A)

**Citations**

10 citations to date (October 2012)

**Study appraisal and star rating**

Methodological quality evaluated by independent reviewers using methods described by Higgins and Altman [564] in the publication:

Wang H, Huang T, Jing J, Jin J, Wang P, Yang M, Cui W, Zheng Y, Shen H. Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. Journal of Hospital Infection 2010;76:1-11.

This was an assessment of all relevant trials on the topic 1996-2009 (428 articles identified, 48 randomised controlled clinical trials included).

Four star rating (maximum 5).

**Biomed Library Rating October 2010**

Top 20 articles published since study publication (see appendix B)

# APPENDIX 1

# APPENDIX 2