Preventing Infections Related to Central Venous and Arterial Catheters

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Wij hålla vth!

Peder Michilsson Hammarskiöld (around 1560-1646)
The Ancestor of the Noble Hammarskjöld Family.
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SAMMANFATTNING PÅ SVENSKA


Artärkatetrar används för blodprovtagning och övervakning av blodcirkulationen inom narkos och intensivvård. Dessa har länge ansetts ge upphov till färre infektioner jämfört med centrala venkatetrar. Studier på senare år har dock visat att så inte är fallet. Infektionsproblematiken för artärkatetrar är endast undersökt i ett fåtal studier och aldrig tidigare i Skandinavien.


De huvudsakliga syftena med avhandlingen har varit att, efter införande av strukturerade hygienrutiner, studera förekomsten av infektioner relaterade till centrala venkatetrar och artärkatetrar. Vi har också varit intresserade av att kartlägga vilka mikroorganismer och riskfaktorer som bidrog till uppkomsten av dessa infektioner. För centrala venkatetrar har vi även önskat kontrollera långtidseffekterna av de strukturerade hygienrutinerna. Slutligen har vi även studerat om det förekom överföring av Candida-stammar mellan patienter som vårdades på vår intensivvårdsavdelning, på samma sätt som är väl visat för ett flertal bakterier.

Resultaten av detta arbete visade att förekomsten (incidensen) av så kallad blodburen infektion associerad med centrala venkatetrar var låg i jämförelse med internationella studier. Den första studien mätte infektioner över 16 månader och omfattade 495 katetrar. Den

I artärtateterstudien, som omfattade 600 kateterar, fann vi inga fall där mikroorganismer från artärtatetern återfanns i blodet. Vi fann dock ett fåtal fall där patienten fått allmänna sjukdomssymptom av mikroorganismer på katetern och dessa fall orsakades samtliga av vita stafylokocker. En riskfaktor för att patienten skulle få artärtateterinfektion var försvagad immunförsvar. Många patienter i studien hade både en artärtateter och central venkateter samtidigt. Det visade sig då att om det växte mikroorganismer på den centrala venkatetern, eller om patienten hade en infektion av denna kateteter, så ökade risken för att patienten även skulle få en artärtateterinfektion. Artärtateterinfektioner var nästan lika vanliga som infektioner relaterade till centrala venkatetrar. Sambandet mellan infektioner på dessa båda katetrar måste vägas in i bedömningen av en patient med infektionssymptom. Vi rekommenderar att man överväger att avlägsna patientens samtidiga centrala venkatetrar och artärtatetrar om en av dessa orsakar en infektion med allmänna symptom. För patienter med långtidssystem, exempelvis venportar och tunnelerade centrala venkatetrar kan andra överväganden behöva göras.

DNA-analys av de 180 funna Candida-stammarna på intensivvårdsavdelningen visade 27 genetiska varianter av arten Candida albicans och tio av arten Candida glabrata. Vissa av de genetiska varianterna återfanns oftare på intensivvårdsavdelningen än i en kontrollgrupp. Detta fynd tillsammans med så kallad klusteralys talade för att det sker en överföring av vissa stammar mellan patienter på intensivvårsavdelningen.
ABSTRACT

Central venous catheters (CVCs) are indispensable in modern medical practice. Serious complications associated with CVC use include catheter-related infection (CRI) and catheter related-bloodstream infection (CRBSI) both of which contribute to morbidity, mortality and healthcare costs. Several studies have shown that implementation of basic hygiene routines, for CVC insertion and care, can significantly reduce the number of CRBSIs. However, there are limited data on the long-term effects after such an intervention. CVC infections, in terms of incidences and microorganisms, vary between different units and countries. Studies from Scandinavian hospitals are rare and not published recently. It has been stated that arterial catheters (ACs) are less prone to be responsible for CRI and CRBSI when compared with CVCs. However, recent studies outside Scandinavia have shown that they cause infections in significant numbers. The general view has been that nosocomial Candida infections in ICU patients evolve from the patient’s endogenous flora. However, a few studies have indicated that transmission of *Candida* spp. can occur between patients on an ICU as is well-described for certain bacteria. *Candida* spp. are among the most common microorganisms responsible for CRI/CRBSI.

The aim of this thesis was to study the incidences of, and microorganisms related to CVC (Study 1) and AC (Study 2) infections after implementation of evidence-based routines for insertion and care. The populations studied were patients with CVCs treated throughout the entire hospital (Studies 1 and 4) and patients with ACs treated on the ICU (Study 2). The aim was further to analyse risk factors contributing to these infections (Studies 1, 2 and 4). We also evaluated the long-term effects and endurance, of evidence-based routines, assessed as temporal variations in CVC colonisation and infections over a six-year period (Study 4). As we found that *Candida* spp. were common causes of CRI/CRBSI in Study 1, we decided to see if transmission of *Candida* spp. possibly occurred between patients on our ICU (Study 3).

We found low incidence rates, compared to international studies, for CRI and CRBSI related to the 495 CVCs studied over a short period (16 months, Study 1) and the 2045 CVCs studied over long-term follow-up (six years, Study 4). We found no cases of AC-CRBSI but a low number of AC-CRI in the 600 ACs studied. The type of microorganisms responsible for infections related to CVCs and ACs were similar to those found in international studies. However, the proportion of *Candida* spp. was high in Studies 1 and 4 evaluating CVC infections. There was no difference in the CVC-catheterisation time for CRI/CRBSI caused by *Candida* spp. as compared to CRI/CRBSI caused by bacteria. Risk factors for CRI associated with CVCs were chronic haemodialysis (Study 1), all haemodialysis in general (Study 4) and CVCs inserted via the internal jugular vein as compared to the subclavian vein (Study 4). Risk factors for CRI related to ACs were colonisation or infection of a simultaneous CVC and immunosuppression. Genotypes of *Candida albicans* and *Candida glabrata* had a heterogeneous distribution between ICU patients over time. Comparison with a reference group and cluster analysis indicated that transmission of *Candida* spp. between ICU patients is possible.

In conclusion, we have found, after implementation of evidence-based routines for CVC and AC insertion and care, low incidences of CRI and CRBSI associated with these catheters. Furthermore, we found that transmission of *Candida* spp. between patients on the ICU is possible.
LIST OF PAPERS


## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AC</td>
<td>Arterial catheter</td>
</tr>
<tr>
<td>AC-CRI</td>
<td>Arterial catheter-related infection</td>
</tr>
<tr>
<td>AC-CRBSI</td>
<td>Arterial catheter-related bloodstream infection</td>
</tr>
<tr>
<td>Apache</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>C</td>
<td><em>Candida</em></td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CFU</td>
<td>Colony-forming unit</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CoNS</td>
<td>Coagulase-negative <em>Staphylococci</em></td>
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<tr>
<td>CRBSI</td>
<td>Catheter-related bloodstream infection</td>
</tr>
<tr>
<td>CRI</td>
<td>Catheter-related infection</td>
</tr>
<tr>
<td>CVC</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>G-charts</td>
<td>Geometrical charts</td>
</tr>
<tr>
<td>I-charts</td>
<td>Individual charts</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>n</td>
<td>Numbers</td>
</tr>
<tr>
<td>NI</td>
<td>Nosocomial infection</td>
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<tr>
<td>NIM</td>
<td>Needles injection membrane</td>
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<tr>
<td>PRCT</td>
<td>Prospective randomised controlled trial</td>
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<tr>
<td>S.</td>
<td><em>Staphylococcus</em></td>
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<tr>
<td>SCHA</td>
<td>0.5% chlorhexidine (w/v) in 70% alcohol</td>
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<tr>
<td>SFAI</td>
<td>Swedish Association for Anaesthesia and Intensive Care</td>
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<tr>
<td>SIRS</td>
<td>Systemic Inflammatory Response Syndrome</td>
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<tr>
<td>Spp.</td>
<td>Species</td>
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<tr>
<td>T-CVC</td>
<td>Tunnelled-central venous catheter</td>
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INTRODUCTION

HISTORY

The first described infusion in man took place in 1667 when a silver cannula was inserted in the antecubal veins, for saline infusion. A pig’s bladder was used as a syringe. During the same year the first successful blood transfusion from lamb to man was performed. However, due to fatal complications, this therapy was banned by the English church and Parliament until 1818. An English obstetrician had then saved several women with severe haemorrhage by injecting human blood, using a syringe.

The first successful attempt to monitor blood pressure was performed in horses in 1773, when glass tubes were inserted into veins and arteries.

It is not fully clear when the first central venous catheterisation was performed. The first paper on central venous catheterisation, performed via the antecubital vein, was supposedly in 1929 by Forssmann, but there are reports as early as 1905 by Bleichroeder. Forssmann proposed, in 1931, that CVCs could be used in emergency situations for rapid delivery of drugs.

Several flexible polyethylene catheters were introduced in the 1940’s which started the general use of intravascular catheters. However several complications such as thrombosis and infections were seen which lead to a continuing search for better catheter materials. This resulted in modern catheter materials such as polyurethane, silicone and Teflon.

The Swedish radiologist, Sven-Ivar Seldinger, published in 1953 his work on a new technique for inserting intravascular catheters. This “catheter over guide-wire” technique was revolutionary and has since become the main technique for CVC insertion throughout the world.

CVCs were predominately inserted via a vein in the upper extremity or the femoral vein, often using a cut-down technique. That is until 1952 when percutaneous infra-clavicular insertion via the subclavian vein was first described. The first descriptions of the supra clavicular approach in the same vein and the internal jugular vein was published in 1965 and 1969, respectively.

The pulmonary artery catheter was first described by Swan and Ganz in 1970. This catheter has since been the gold standard for advanced haemodynamic monitoring. The first Swedish description, to our knowledge, of the pulmonary artery catheter in humans was from Jönköping in 1980.

To overcome the problems of infections and mechanical problems associated with long-term venous access for parenteral nutrition and chemotherapy, new silicone catheters (i.e. Broviac and Hickman catheters) were introduced in the Seventies. These were flexible t-CVCs with a subcutaneous cuff. Surgically implanted subcutaneous ports were first described in 1982 and are preferred for long-term chemotherapy and parenteral nutrition.
To increase the safety of CVC insertion ultra-sound guidance was proposed in 1982 and has now become an established technique for the insertion of CVCs.

Since the beginning of the Seventies there has been increasing focus on preventing CVC infections. Maki has been the leading light in this field and has contributed much to our present knowledge concerning strategies for the prevention of infections. The most well-known guidelines for prevention of CVC-infections were, to our knowledge, published in a first edition by CDC in 1983.

There has been a considerable amount of research in this field throughout the world, and over the two last decades there has been a revolution in the care of patients with intravascular access. New catheters, ultrasound-guided insertion and improved hygiene routines have increased the safety for patients with a CVC, and since 2010, a world congress on vascular access has been organised every second year (www.wocova.com).

NOSOCOMIAL INFECTIONS

The evolution of modern medical care has increased our ability to treat severe and advanced medical conditions. This progress has accelerated over recent decades and many patients, who were previously beyond therapy, can now be treated and cured.

Simultaneously, there has been an awakening to the problem of hospital-acquired infections, so-called nosocomial infections (NIs). NIs, to a large extent, affect vulnerable patients such as those with advanced chemotherapy, after surgery, on intensive care, with implanted foreign bodies (i.e. orthopaedic prostheses, and intravascular devices) and after transplantation, immuno-compromised patients, and neonates. Misuse of antibiotics, crowded and understaffed wards, insufficient adherence to hygienic-routines, and transportation of patients between units are also realities that increase the risk for NIs.

The most common NIs are surgical wound infections, urinary tract infections, intravascular device infections (i.e. catheters and pacemakers), pneumonia including ventilator-associated pneumonia, antibiotic-associated diarrhoea, and prosthesis infections (i.e. orthopaedic and vascular-). Unfortunately, NIs are closely related to the increasing problem of multi-resistant microorganisms.

The incidence of NIs and type of microorganisms involved vary greatly between similar units depending on patient population, geographical location, adherence to hygiene routines, use of antibiotics etc. Furthermore, the incidence and microorganisms involved can vary over time within the same unit.

It is obvious that NIs contribute to morbidity, mortality and enormous healthcare costs. Several studies have shown that these complications can, to a large extent, be avoided using various approaches that have been shown to reduce morbidity, mortality and healthcare costs.

The medical profession has to engage several strategies to prevent NIs and antibiotic resistance. These include well-functioning basic hygiene routines in all aspects of medical care, the rationale use of antibiotics, special medical techniques/routines in highly vulnerable
situations, thorough clinical evaluations of previously known factors and research. Most of these strategies should be well-known in view of the efforts made to spread knowledge. In spite of this, international studies have shown that there is surprisingly low knowledge and adherence to the guidelines and education programmes that substantially reduce the incidences of NIs. Over recent decades many authorities in the West have focused attention on this problem, examples of this including USA: save 5 million lives campaign (www.ihi.org), Europe: the ECDC (www.ecdc.europa.eu) and Sweden: Swedish Strategic Programme against Antibiotic Resistance (www.strama.se) and campaigns launched by The Swedish Association of Local Authorities and Regions (www.skl.se).

CENTRAL VENOUS CATHETERS

Background

Modern medical care is highly dependent on vascular access for treatment and monitoring. Peripheral venous catheters, predominately inserted in the veins of the upper extremity, are the most commonly used catheter for intravascular injections and infusions. Peripheral venous catheters are rarely responsible for serious NIs, the reasons for this could be the relatively short catheterisation time.

In certain circumstances a peripheral venous catheters is insufficient and has to be replaced by a CVC which is an intravenous catheter with the tip positioned in the central circulation. The CVC is usually inserted via the internal jugular or subclavian vein but the femoral vein and the veins of upper extremity are also used.

Indications

The indications for a CVC are numerous:

- Intravenous therapy with large amounts of fluids over a short-term, i.e. trauma, surgery, ICU treatment.
- Intravenous administration of vascular irritant drugs and solutions with high osmolarity.
- Intravenous treatment over a long-term period (> 4 weeks), i.e. parenteral nutrition, antibiotics, chemotherapy, blood products.
- Repeated blood sampling over a long-time
- Haemodynamic monitoring during intensive care and anaesthesia.
- Haemodialysis

Choice of catheter

Modern CVCs are made of polyurethane or silicone. Neither of these is superior in preventing CVC infections and the choice of material is predominantly based on mechanical preferences. Over the last ten years there has been an evolution of CVCs treated with various antimicrobial substances (antibiotics, antiseptics) or other substances that inhibit microorganisms adhering and growing on a CVC. There have also been trials using low current and ultraviolet light, but these methods are not yet ready for clinical use. Only
catheters impregnated with chlorhexidine/silver-sulfadiazine or minocycline/rifampin have, until now, been shown to be effective in PRCT\textsuperscript{17}. There are those who claim that these two catheters carry the risk for increased microbial resistance. These fears, however, have not been founded\textsuperscript{18}. However, these catheters can never replace insufficient hygiene routines.

Depending on what the CVC is to be used for, there are several kinds of catheters. The catheter can contain one to several lumina (=channels), depending on the number of infusions that the patient requires simultaneously, or concomitant haemodynamic monitoring. The calibre of the catheters varies widely depending on the amount of flow required. The length of the catheter is often between 15 and 25 cm but can be up to 80 cm, as for example, the pulmonary artery catheter. The catheters are inserted through the skin and the subcutaneous tissue into the vessel. The subcutaneous part may be deliberately prolonged (> 5-10 cm) and this is called a tunnelled-CVC (t-CVC). This technique has been shown to be effective in reducing the number of CVC infections when the catheters are inserted via the internal jugular or femoral vein\textsuperscript{19,20}. A t-CVC can be attached to a surgically implanted subcutaneous infusion chamber. This system is called a subcutaneous venous port. Infusions using this system are achieved via a special needle that is forced through a silicone diaphragm that lies just below the skin.

**Figure 1:** Examples of central venous catheters and an arterial catheter (from top: pulmonary artery catheter, single lumen central venous catheter, four lumen central venous catheter, subcutaneous venous port, arterial catheter and central dialysis catheter).
The CVC are often divided accordingly:

1. Single or multi-lumen catheters: narrow catheters for short-term use on the wards, ICUs and during anaesthesia (Figure 1). Multi-lumen catheters may have an increased risk for CVC infections and the number of lumina should be kept to a minimum.21
2. Tunnelled single or multi-lumen catheters: relatively small gauge catheters predominately used for long-term infusion for parenteral nutrition or chemotherapy outside the hospital.
3. Non-tunnelled (Figure 1) and tunnelled-CVCs for haemodialysis: relatively large calibre catheters which are used for short and long-term haemodialysis.
4. Pulmonary artery catheters (Figure 1): long small gauge catheters used for advanced haemodynamic monitoring.
5. Peripherally inserted CVCs, termed PICCs: long small gauge catheters inserted via a vein in the upper extremity, predominately for chemotherapy but have also gained popularity in the acute care setting and for parenteral nutrition.
6. Subcutaneous venous ports (Figure 1): aimed for long-term treatment outside the hospital, and used for chemotherapy, blood products, and parenteral nutrition.

**Insertion**

Several studies have shown that the number of complications, including infections, secondary to CVC insertion, are decreased if performed by a well-trained operator.22 Hence, the operator should be fully trained and beginners should insert catheters under supervision and preferably perform their first insertions on dummies.23-26 All CVC insertions should be performed according to a checklist and be fully documented.14

In recent years substantial evidence has been gained that real-time ultrasound insertion decreases the mechanical complications associated with CVC insertion. This is especially so for the internal jugular vein, but also for the subclavian and femoral veins.27-29 It has not been shown, however, that ultrasound insertion affects the incidence of CVC infections.

Insertion of a CVC should preferably be performed in a location intended for surgery. Unfortunately, due to clinical considerations, this is not always possible and therefore the procedure is often performed in such places as the emergency department and ICU.

The person inserting the CVC should be dressed with maximal sterile precautions, which includes sterile gloves, hat, mask and sterile gown. Furthermore the patients should be well covered by large sterile drapes.30-32

The insertion site should be carefully treated with a disinfection solution prior to insertion. Several different solutions have been used alone or in combination for this purpose. However it has been shown that the most effective solution in preventing CVC infections is SCHA.33-35 The optimal concentration of chlorhexidine has to be evaluated in further studies, and currently there are different solutions between 0.5 and 2%. The effect of a preoperative chlorhexidine shower or bath, which is frequently a recommended procedure to prevent surgical site infection, is scarcely studied.36

Prophylactic antibiotics should not be used as a routine, but may be considered under special circumstances such as in patients with neutropenia and complicated insertion.37
CVC for short-term use should be secured with monofilament sutures. New commercial suture-less devices have not been evaluated in PRCTs. The insertion site should be covered with sterile gauze or a semi-permeable polyurethane dressing. Polyurethane dressings or sponges containing chlorhexidine could, decrease the risk for CVC infections even further.

Catheter care and removal

All handling of the catheter should be performed under sterile conditions. A checklist could be a valuable tool for the procedure and its documentation. The CVC and the insertion site should be inspected every day for complications and the need for the catheter should be questioned. The CVC should promptly be removed when it is no longer required.

Several ICU studies have demonstrated a lower CRBSI incidence if a daily whole body wash with chlorhexidine is performed. Most studies, but not all, have shown a reduction in CVC colonisation or infections when using NIMs. To gain the positive effect of using these devices it is mandatory that they be used according to instructions. This includes using NIMs of split-septum type and scrubbing the membrane ("scrub the hub!") with SCHA before each use.

Connectors, valves, lines and NIMs should be changed every third day for inpatients and, at least every seventh day for outpatients. This time-interval for CVCs in patients getting blood products or lipid solutions is controversial. Studies dealing with this problem are conflicting and some recommendations, based on old studies, advocate a time interval of only one day if these solutions are to be used.

CVC dressings should be changed at least every fifth day and more often when necessary. Outpatients usually, for practical reasons, have their dressing changed every seventh day. During the change should the insertion site be treated with SCHA.

T-CVCs should have dressings, changed as above, until the subcutaneous cuff has firmly healed and the sutures have been removed.

CVCs should be flushed with saline after each use and the catheter should be filled with this solution, while not in use. Heparin has traditionally been used as a lock solution to prevent occlusion, trombosis and possibly also infections. No well-designed studies support this. However, there are some new lock solutions that are promising either alone or in combination. These are hydrochloric acid, ethanol, methylene blue, vancomycin and several other antimicrobial drugs.

The older routines of changing CVC once a week to prevent infections has not been shown to be successful. CVC-exchange over a guide-wire can be performed in the case of CVC malfunction or switch to another CVC-type. This implies a decreased risk for mechanical complications, even though microorganisms can be transferred to the new catheter. Hence, change over guide-wire is not suitable when there is a local infection or high suspicion of CRI/CRBSI. CVC-exchange over a guide-wire should be performed under the same sterile precautions as insertion at a new site.
Local guidelines for central venous catheter insertion and care.

In 1998 the Department of Anaesthesia and Intensive Care in Jönköping started a quality improvement programme with the aim of optimising the insertion and care of CVCs and ACs to achieve low infection rates related to these catheters. This resulted in a document which described the problem, defined the infections, and established evidence-based routines for catheter insertion and care. All staff participated in the education programmes and was obliged to follow these recommendations that, with minor revisions, have been used ever since.

Table 1 summarises the evidence-based recommendations used at the Jönköping Hospital for CVC insertion and care. These recommendations are now also national guidelines, presented by SFAI (www.sfai.se), the Swedish Association of Local Authorities and Regions (www.skl.se), and the Handbook for Healthcare (www.vardhandboken.se).
Table 1: The evidence-based recommendations from Jönköping for central venous catheter insertion and care.

General remarks
Implement full adherence to basic hygiene routines
Organise a CVC team on every unit that inserts and uses CVCs
Create evidence-based routines for insertion and care of CVCs
Perform regular education on CVC insertion and care
Document insertion and care of CVCs in standardised documents
Monitor adherence to basic hygiene routines
Monitor adherence to CVC routines
Monitor incidence of CVC infections over time

Routines for CVC insertion
Only use CVCs on correct indications
Use ultrasound guidance when possible
Use the most suitable vessel for each patient and take both mechanical and sterility considerations
Treat the insertion site with SCHA solution prior to insertion
Use maximal sterile precautions
Use CVCs with as few lumina as possible
Use sutures for fixation
Cover insertion site with sterile gauze or semi-permeable dressing
Insert tunnelled CVC or subcutaneous venous port for catheterisation time >3-4 weeks

Routines for CVC care
Evaluate the need for the CVC every day
Examine the CVC for complications at least once day.
Change dressings every 1-5 days (every 7th day in outpatients)
Change sterile dressings under sterile conditions
Clean the insertion site with SCHA solution when dressing is changed
Use NIMs for all injections
Clean and scrub the NIM with SCHA solution prior to each use (“scrub the hub”)
Flush the CVC with saline repeatedly after each use to prevent occlusion
NIMs, hubs and infusion lines should be changed every third day (every 7th day in outpatients)
Lipid solutions should be administered in a separate lumen if a multi-lumen CVC is used.
A CVC can be used for blood transfusion and blood sampling.
CVC exchange due to malfunction, or to another CVC-type should be performed over a guide-wire, whenever possible
Remove the CVC when it is no longer needed

Additional options to decrease CVC infections in selected situations
Consider antimicrobial CVCs
Consider chlorhexidine sponges
Consider semi-permeable films containing chlorhexidine
Consider antimicrobial lock solutions
On the ICU: consider daily whole body wash with chlorhexidine

CVC: Central venous catheter
SCHA: 0.5% chlorhexidine (w/v) in 70 % alcohol
NIM: Needless injection membrane
ICU: Intensive care unit
ARTERIAL CATHETERS

Background and indications

ACs are mainly inserted for repeated blood sampling, including arterial blood gases, and intravascular haemodynamic monitoring during advanced anaesthesia and ICU treatment. Contrary to the number of studies on CVCs there are very limited data on ACs in terms of catheter care, complications and their risk factors. Therefore, most routines are extrapolated from studies on CVCs.

Choice of catheter

ACs are non-antimicrobial, single lumen catheters made of polyurethane or Teflon.

Insertion

ACs are mostly inserted in the radial or femoral artery, but other arteries such as the ulnar, brachial and dorsalis pedis artery are also used. Contrary to CVCs, which are mainly inserted using the Seldinger technique, ACs are inserted with a catheter over cannula (as peripheral venous catheters), or Seldinger technique.

One study has evaluated the use of maximal sterile precautions during insertion of an AC. This showed no advantage regarding infectious complications when compared with the use of sterile gloves and ordinary hospital clothing only. The insertion site should be treated with SCHA prior to insertion and the operator should wear sterile gloves. Sterile drapes may be considered, especially for insertion in the femoral artery.

Ultrasound guidance when inserting ACs is much less studied than with CVCs. However some studies have shown that this technique enhances the success rate. ACs are secured with sterile stripes or monofilament sutures. The insertion site should be covered with sterile gauze or a semi-permeable polyurethane dressing.

A blood sampling pressure set containing saline is always connected to the AC. New closed sampling pressure sets have been shown to reduce the need for blood transfusion in patients staying on the ICU for a long time. Microbial colonisation seems to be reduced with these systems but no study has evaluated the effect on AC infections. Furthermore, closed sampling sets reduce the chance of staff coming into direct contact with the patient’s blood.

Catheter care

All handling of ACs should be performed under the same sterile conditions as with CVCs. A checklist is a valuable tool for the procedure and its documentation. The AC and the insertion site should be inspected every day for complications and the need for the catheter should be questioned. The AC should promptly be removed when it is no longer required.

It is recommended that the blood sampling pressure sets and dressings are changed every second to fourth day and the insertion site should be treated with SCHA.
INFECTION COMPLICATIONS RELATED TO THE USE OF CENTRAL VENOUS CATHETERS AND ARTERIAL CATHETERS.

Mechanisms

The mechanisms of infectious complications from intravascular catheters are often divided in three categories (Figure 2):72:

1. Cutaneous spread of microorganisms from the skin on the outside of the catheter during or after insertion.
2. Contaminated infusate, hubs and lines, commonly caused by inappropriate handling.
3. Haematogenous spread of microorganisms.

The two first mechanisms are probably the most common causes of catheter infections and can to a large degree be prevented by high adherence to structured hygiene routines. The third mechanism and can only be prevented by the use of anti-microbial catheters.

**Figure 2:** Causal factors of central venous catheter-related infections. Reprinted, with permission, from the Centers for Disease Control and Prevention.72
Definitions

The difficulties in diagnosing CVC infections have over the years resulted in a variety of definitions which has to be considered in the evaluation and comparison of scientific studies on infectious complications. Traditionally these infections have been divided into local infections around the insertion site or the subcutaneous tract and bloodstream infections. The first two are diagnosed by inspection and local cultures and the third by tip and blood cultures in patients with signs and symptoms of general infection. The problem with this categorisation is that most CRI/CRBSI show no local changes and cultures can be falsely negative or positive. To overcome this problem, a third definition has been proposed including positive tip culture, signs and symptoms of general infection where there is no other obvious source of infection. However this definition carries the risk of falsely categorising a CVC colonisation as an infection when there is a non-CVC explanation for the patient’s symptoms. Hence, we propose the following definitions for CVC colonisation and infection:

Colonisation
Microbial growth on the catheter tip.

Local infection
Inflammation or pus at the insertion site with a positive culture from the site or the subcutaneous tract.

Catheter-related infection (CRI)
Positive CVC tip culture with symptoms of systemic inflammation and no other obvious source of infection.

Catheter-related bloodstream infection (CRBSI)
Indistinguishable microorganisms are isolated from peripheral blood and the catheter tip or blood taken via the CVC.

Systemic inflammation
The definition mostly used for general infection in the diagnosis of CVC-infections has included fever, chills and hypotension. However, most CVCs are used in ICU or immune-compromised patients and these symptoms can be present or absent depending on the illness or its treatment (i.e. leukopenia, steroid treatment, haemodialysis, inotropes, induced hypothermia, sedation, and muscle relaxants). It is our opinion that the well-established definition of systemic inflammation in the ICU setting, the so-called Systemic Inflammatory Response Syndrome (SIRS) is a better alternative when evaluating patients with suspicion of CVC infection. SIRS caused by an infection is called sepsis, and with increasing severity it is further divided into severe sepsis and septic shock (Table 2).

Unfortunately, there is no absolute consistency in the definition of CVC infections (Table 3). Furthermore, it has also been shown that several studies have referred to the same original definition but have used it in a modified way. These factors have to be considered when comparing different studies.
Table 2: Criteria for the Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis and septic shock:

**SIRS**

At least two of the following symptoms:
- Body temperature >38°C or <36 °C
- Heart rate >90 beats per minute
- Respiratory rate >20 per minute PaCO2 <4.3 kPa
- B-Leukocytes >12x10^9/l or <4x10^9/l, or >10% immature granulocytes

**SEPSIS**

SIRS caused by microorganisms

**SEVERE SEPSIS**

Sepsis associated with organ dysfunction.

**SEPTIC SHOCK**

Sepsis with refractory hypotension or hypoperfusion abnormalities despite adequate fluid resuscitation.
Table 3: Our simplified comparison of four definition systems regarding central venous catheter infections.

<table>
<thead>
<tr>
<th>CDC*</th>
<th>IDSA**</th>
<th>ECDC</th>
<th>SFAI**</th>
<th>This thesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colonisation</strong></td>
<td>&gt;15 CFU on tip culture</td>
<td>≥1 CFU on tip culture</td>
<td>Positive tip culture (≥10³ CFU/ml or ≥15 CFU)</td>
<td>Positive tip culture without clinical symptoms</td>
</tr>
<tr>
<td><strong>Local infection</strong></td>
<td>Exit site local infection: Inflammation (without pus) &lt;2 cm at insertion site(^a)</td>
<td>Clinical exit site local infection: Inflammation &gt;2 cm and pus at insertion site(^a)</td>
<td>Microbial exit site: Exudate at exit site and positive local culture(^b)</td>
<td>Positive tip culture (≥10³ CFU/ml or ≥15 CFU) and pus/inflammation at insertion site</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>CVC-related infection</strong></td>
<td>Exit site local infection: Inflammation (without pus) &lt;2 cm at insertion site(^a)</td>
<td>Clinical exit site local infection: Inflammation &gt;2 cm at insertion site(^b)</td>
<td>Microbial exit site: Exudate at exit site and positive local culture(^b)</td>
<td>Positive tip culture (≥10³ CFU/ml or ≥15 CFU) and pus/inflammation at insertion site</td>
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</tr>
<tr>
<td><strong>CVC-related bloodstream infection</strong></td>
<td>Positive peripheral blood culture in a patient with a CVC and symptoms(^d) of systemic inflammation and no other obvious source of infection</td>
<td>One of the following should also be present: Positive tip culture (semi-quantitative or quantitative) with the same (antibiogram) microorganism or positive paired blood culture</td>
<td>Positive tip culture and blood culture performed 48 h prior or after insertion with same microorganisms or positive paired blood culture</td>
<td>Positive tip culture and blood culture performed 48 h prior or after insertion with indistinguishable (antibiograms) microorganisms or positive paired blood culture</td>
</tr>
</tbody>
</table>

\(^a\) Can be associated with BSI

\(^b\) In the absence of concomitant BSI

\(^c\) Fever, chills and hypotension

\(^d\) Two out of four SIRS symptoms

\(^e\) Two out of four SIRS symptoms

*www.ecdc.europe.eu

**www.sfai.se
CDC: Centers for Disease Control and Prevention
IDSA: Infectious Diseases Society of America
ECDC: European Centre for Disease Prevention and Control
SFAI: Swedish Association of Anaesthesia and Intensive Care
CFU: Colony-forming units
BSI: Bloodstream infection
CVC: Central venous catheter
SIRS: Systemic Inflammatory Response Syndrome
Culture methods

Tip culture
The dominating method for culture of intravascular catheter tips has, since 1978, been the roll-plate method described by Maki\textsuperscript{78}. This method is considered positive when $\geq 15$ CFU are isolated. The problem with this method is that it predominately cultures microorganisms from the external surface on the catheter and not the internal lumen. To overcome this problem an alternative method has been developed which also cultures microorganisms from the interior lumen of the catheter and is considered positive when $>10^2$ or $10^3$ CFU per ml\textsuperscript{79}. However, there are no data that clearly show one culture method to be superior to the other\textsuperscript{80-82}.

The tip culture method has several limitations.
- The catheter has to be removed for culture.
- The distinction between catheter colonisation and infection can be difficult.
- The culture results can be influenced by antimicrobial treatment culture technique, transportation and time\textsuperscript{77,80,83}.
- There has been little evaluation of tip culture techniques for antimicrobial CVCs.
- There are limited data on culture cut-off values for different microorganisms.

Blood culture
Since CRBSI has been the standard for diagnosing intravascular catheter infections, a blood culture is mandatory. A blood culture drawn from a catheter can reflect colonisation and therefore a simultaneous sample from another vessel has to be performed to verify that the microorganism has spread to the blood. However, haematogenic spread of microorganisms will, of course, regardless of focus give positive blood cultures from a vessel or a catheter. Therefore, blood cultures taken for the diagnosis of CRBSI should be performed as follows:

- Perform \textit{paired blood culture} i.e. simultaneous blood cultures from the CVC and another vessel\textsuperscript{84,85}
- The paired blood culture is considered positive for the CRBSI diagnosis if blood culture from the CVC is positive $>120$ minutes before the peripheral blood culture\textsuperscript{86} or the ratio between CVC and peripheral blood is $3-5:1$ CFU/ml\textsuperscript{87}.

The blood culture method has several limitations.
- Blood samples must be taken through all the lumina in a multi-lumen CVC\textsuperscript{88}.
- The culture results can be influenced by antimicrobial treatment, culture technique, and transportation time\textsuperscript{80,89}.
- Microorganism can be intermittently released to the bloodstream
- There are limited data on culture cut-off values for different microorganisms concerning analyses of time to positivity or CFU per ml.
- Microorganisms found on tip and blood cultures are regarded as indistinguishable if phenotype and antibiograms are equal. This may not be correct since different genotypes of the same phenotype could have the same antibiogram.

Culture in daily practice
Since tip- and blood cultures have limitations both methods must be available for clinical assessment of a patient with CVC infection symptoms. Unfortunately, cultures can be falsely positive or negative. The patient’s symptoms may be depressed by illness or treatment and therefore a unique clinical judgement has to be performed in every situation, evaluating both
culture results and clinical signs. Both CRI and CRBI are valuable entities in patient care and for monitoring infectious complications related to CVCs.

Microbiology

There is a myriad of microorganisms reported to cause CRI/CRBSI. However, the most common agent is CoNS followed by S. aureus and Candida spp. Other microorganisms that should be considered are gram negative rods and Enterococcus spp.

Diagnosis and treatment

The questions that have to be answered in a patient with a CVC and infection symptoms are:

1. Is the CVC responsible for the patient’s infection symptoms?
2. Should the CVC be removed?

The ability to answer the question of the catheter’s role in the patient’s symptomatology is influenced by several different factors and it is not always possible to arrive at a correct answer. In severely ill patients on several antibiotics and where there is no possibility to wait for cultures, the only alternative is to remove the catheter and treat the patient. In ICU patients with short-term catheters this is not a problem since it is usually easy to remove the catheter and insert a new. However, in patients with long-term access this may not be so easy.

There are limited data, from PRCTs, on treatment strategies for infectious complications related to CVCs and most data are based on “expert opinion”. However, a useful approach to management is to ask the following questions:

1. Has the patient severe sepsis or septic shock?
2. Does the patient need the CVC?
3. Is the CVC a short- or long-term catheter?

Thereafter, following treatment strategies are applicable in patients with a CVC and symptoms of infection:

Short-term catheters, both CVCs and ACs:

Local infection without other clinical symptoms
- Remove the catheter and perform culture from blood, insertion site and catheter tip. Consider administering systemic antibiotics. Positive tip culture strengthens the indication for antibiotics.

Non-infected insertion site
- Severe sepsis or septic shock: remove the catheter and take culture samples from blood, insertion site and catheter tip. Administer systemic antibiotics.
- Sepsis (but not severe sepsis or septic shock) and suspicion of CRBSI: remove the catheter and take culture samples from blood and catheter tip or change the catheter over a guide-wire and take culture samples from blood and catheter tip. Consider systemic antibiotics. Alternatively, perform paired blood cultures with the catheter in situ. Consider systemic antibiotics.
If cultures confirm the CRI/CRBSI diagnosis the CVC has to be removed and a new catheter should be inserted at a new insertion site. There are no data evaluating the routine to wait a day or longer before inserting a new CVC after that an infected catheter has been removed.

Long-term catheters (tunnelled CVCs and subcutaneous venous ports):

- **Severe sepsis or septic shock, with or without local infection**: perform paired blood culture and take culture samples from insertion site and subcutaneous tract. Remove the catheter and perform tip culture. Give systemic antibiotics.
- **Sepsis (but not severe sepsis or septic shock), with or without local infection**: perform paired blood cultures and take culture samples from insertion site or subcutaneous tract. Administer antibiotics and wait for culture results. If cultures reveal *S. aureus* or *Candida* spp., then remove the catheter. Continue with suitable antibiotics. For other microorganisms watchful treatment, with a catheter *in situ*, is allowed. In case of unsuccessful treatment or relapse of infection the catheter should be removed. Antimicrobial lock treatment could be considered as an adjuvant treatment for catheters *in situ*.

PRCTs have not addressed the length of antibiotic treatment for CRI/CRBSI. However, the general agreement is as follows:

- **S. aureus**: systemic antibiotics for at least 14 days. Consider periods of 4-6 weeks for long-term systems.
- **Candida species**: systemic antifungals for 14 days after first negative blood culture.
- **Other species**: systemic antibiotics for 7-14 days.

If the CRBSI is complicated by endocarditis, osteomyelitis, infected thrombosis etc. the treatment period has to be prolonged.

SFAI (www.sfai.se) has developed treatments algorithms, adopted from IDSA77, for suspected CVC infection in short and long-term catheters. These are presented in Figures 3 and 4.
Figure 3: Suggested management of infections associated with short-term CVCs. Solid arrows indicate positive and dashed arrows negative answers (www.sfai.se).
Figure 4: Suggested management of infections associated with long-term CVCs. Solid arrows indicate positive and dashed arrows negative answers (www.sfai.se).

Suspected/verified long-term CVC related infection

Is CVC needed?

Severe sepsis, septic shock or infectious complication (endocarditis, osteomyelitis, epidural abscess, septic thromboembolism)?

- Coupled blood cultures
- Remove CVC
- Catheter tip culture
- Swab culture tunnel/pocket
- Give appropriate antibiotics
- Adjust antibiotics according to cultures

Growth of Staphylococcus aureus or Candida albicans?

- Coupled blood cultures
- Swab culture from tunnel/pocket
- Give appropriate antibiotics
- Consider lock therapy

Insufficient or recurrent signs of infection during/after antibiotic treatment?

- Remove CVC
- Catheter tip culture
- Swab culture from tunnel/pocket
- Adjust antibiotics according to cultures
Epidemiology, mortality and healthcare costs

The number of CVCs used in Sweden every year is estimated by SFAI to be around 50,000 (www.sfai.se). There are no data on the nationwide number of infectious complications related to these catheters. In the United States there is an estimation of around 80,000 CRBSIs every year\(^7\).

The CRBSI rate varies significantly in different studies, depending on several factors such as patient groups, type of unit, catheter type, adherence to hygiene strategies, and definitions used. The regular view has been that ACs are seldom responsible for catheter-related infections\(^90-91\). However, a few recent studies have suggested that they do occur in significant numbers, comparable with CVCs\(^92-94\). Pooled incidence figures for CRBSI with different intravascular devices are showed in Table 4\(^95\).

<table>
<thead>
<tr>
<th>Type of catheter</th>
<th>Number of studies</th>
<th>Incidence (mean) per 1000 catheter-days</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral venous catheter</td>
<td>110</td>
<td>0.5</td>
<td>0.2-0.7</td>
</tr>
<tr>
<td>Arterial catheter</td>
<td>14</td>
<td>1.7</td>
<td>1.2-2.3</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>13</td>
<td>3.7</td>
<td>2.4-5.0</td>
</tr>
<tr>
<td>PICC</td>
<td>15</td>
<td>1.1</td>
<td>0.9-1.3</td>
</tr>
<tr>
<td>Non-tunnelled CVC (not antimicrobial)</td>
<td>79</td>
<td>2.7</td>
<td>2.6-2.9</td>
</tr>
<tr>
<td>Non-tunnelled CVC (Ch/s)</td>
<td>18</td>
<td>1.6</td>
<td>1.3-2.0</td>
</tr>
<tr>
<td>Non-tunnelled CVC (M/r)</td>
<td>3</td>
<td>1.2</td>
<td>0.3-2.1</td>
</tr>
<tr>
<td>Cuffed and tunnelled-CVC</td>
<td>29</td>
<td>1.6</td>
<td>1.5-1.7</td>
</tr>
<tr>
<td>Non-tunnelled dialysis catheter</td>
<td>16</td>
<td>4.8</td>
<td>4.2-5.3</td>
</tr>
<tr>
<td>Cuffed and tunnelled dialysis catheter</td>
<td>16</td>
<td>1.6</td>
<td>1.5-1.7</td>
</tr>
<tr>
<td>Subcutaneous venous port (central)</td>
<td>14</td>
<td>0.1</td>
<td>0.0-0.1</td>
</tr>
</tbody>
</table>

CI: Confidence interval
PICC: Peripherally inserted central venous catheter
CVC: Central venous catheter
Ch/s: Chlorhexidine/Silver-sulfadiazine
M/r: Minocycline/rifampin

True analysis of the healthcare cost of CRBSI is difficult\(^96\). Increased costs are due to prolonged hospitalisation, drugs, supplies, lab tests and specialist visits. Estimations from the United States have shown an increased cost of 10,000-45,000$ per CRBSI\(^96-98\). Studies from Europe have demonstrated costs of approximately 10,000 €\(^99\). Unpublished data from the ICU at the Sahlgrenska University Hospital in Gothenburg have shown a 200,000 SEK increase in ICU cost for each CRI (personal communication, Sophie Lindgren, PhD, Senior Consultant).

The direct mortality caused by CVC infections has been difficult to define and mortality rates in international studies vary between zero and 25%\(^16\) 100-102.
Hygiene strategies, CVC teams and evaluation

Several studies have shown that implementing simple basic hygiene routines can significantly reduce the number of CRBSI\(^{109-106}\). Most of these studies have focused on ICUs and other patient groups of with special risk for CRBSI. A few studies have also been able to show that these efforts will reduce the CRBI incidence over sustained periods of time\(^{103,105,108}\). One study has also indicated that the concept decreases overall mortality\(^{107}\). It is therefore fundamental that all units were CVCs are inserted or used have a CVC team\(^{22,32,108}\). These teams should implement evidence-based strategies and run continuous education if one is to decrease the number of infectious complications secondary to CVCs. This includes basic strategies for insertion, care and handling of complications. Furthermore, there must be a continuous evaluation programme on adherence to routines and follow-up of complications\(^{32}\).

CANDIDA TRANSMISSION

Background

Candida colonisation and invasive fungal infections, especially with Candida spp., have increased in the ICU setting throughout the world over the recent decades\(^{109}\). Furthermore, there has been an increased focus on Candida spp., causing infections and not only colonisation. The reasons for this increasing problem are probably the advances in medical technology, i.e. transplantation, chemotherapy, advances in surgery and intensive care, invasive catheters, use of broad-spectrum antibiotics, and haemodialysis. Most of these infections are caused by C. albicans. Unfortunately, there has been an increase in the frequency of fluconazole-resistant species, especially C. glabrata\(^{109}\).

There are several risk factors for Candida infections on the ICU, i.e. surgery, total parenteral nutrition, fungal colonisation, renal replacement therapy, infection and/or sepsis, mechanical ventilation and high Apache II/III\(^{110}\). Furthermore, blood stream infections with Candida spp. increase length of stay, mortality, and healthcare costs\(^{109}\).

Transmission

The transmission of pathogenic bacteria between patients on an ICU is well documented\(^8\), but the role of this mechanism in the case of Candida spp. has not fully been explored and previous studies have shown conflicting results\(^{111-118}\). Traditionally it has been stated that fungal infections evolve from the patient’s endogenous flora, especially from the gastrointestinal tract\(^{119}\). However, a few studies have indicated transmission between patients within the ICU and the neonatal ward\(^{111-114,116,117,120}\). It has also been shown that healthcare workers carry fungal species on their hands\(^{111,112,121}\) and nosocomial outbreaks have been reported\(^{113,122}\).

The study of transmission is complex and depends on several factors:

1. Candida colonisation varies significantly in different reports, depending on several factors such as diagnosis, type of surgery, length of ICU stay as well as selection of culture sites and sampling techniques\(^{118}\).
2. Analysis of relation between isolates demands DNA-analysis which is complex, time consuming and expensive, especially for multi-locus sequence typing, which is the standard method. This method can now in the clinical setting be replaced with simplified techniques such as the rep-PCR method, which is commercially available, DiversiLab (bioMérieux, Marcy l’Etoile, France)

3. Since variations of Candida spp. genotypes in different populations, at specific times, not are known, statistical support of transmission is complex. A higher incidence of a specific genotype in simultaneous patients at a specific time could be explained by natural variations within the population, and is not necessarily caused by transmission. Statistical analysis of transmission within a unit demands cluster analysis, and temporal cluster analysis has never been attempted on Candida transmission.

4. A reference group is difficult to define since it will demand a similar case mix of patients regarding age, medical treatments, immune status, surgery, antibiotics and geographical location. Two identical ICUs in different geographical locations will not necessarily have the same genotypes or variations in genotypes over a specified time period. The same problem exists when using healthy people outside the ICU or patients within the same hospital but outside the ICU. A suitable reference group could be patients with blood cultures positive for Candida species outside the ICU. This patient group represent a cohort of severely ill patients from the same geographical area as the ICU patients.

PREVENTING NOSOCOMIAL INFECTIONS ON THE INTENSIVE CARE UNIT IN JÖNKÖPING

In 1998 the ICU in Jönköping started several healthcare quality improvement programmes with the aim of improving all aspects of critical care and reducing complications, including NIs. This resulted in documents describing the problems, defining various infections, and introduction of several evidence-based routines for patient care which could influence the incidence of NIs.

There was also the implementation of systems evaluating the incidence of complications including NIs, microbiological epidemiology, and antibiotic use and resistance. The cornerstones of this concept are summarised in Table 5.

Continuous assessment of different outcome data has indicated that the overall programme on the ICU has been successful in terms of low incidence of NIs. Registered nosocomial infections in the ICU between years 2000 and 2012 are presented in Table 6.
Table 5: The Jönköping intensive care unit concept for preventing nosocomial infections

**Staffing**
High continuity of well-educated ICU-physicians.
Adequate nurse: patient ratio.
All nurses have critical care education.

**Preventive strategies**
Thorough routines for patient care and hygiene precautions.
Isolation of patients with suspected or verified multi-resistant bacteria.
Daily visiting infection specialist.
Continuous collaboration with the Department of Microbiology.

**Education**
Educational programmes to increase the awareness of nosocomial infections.
Educational programmes on the prevention of nosocomial infections, including insertion and care of central venous catheters.

**Evaluation**
Weekly surveillance cultures from all patients with an ICU stay >72 hours.
Evaluation of routines by the hospital’s Department of Hygiene.
Continuous evaluation of patient outcome and overall complications.
Continuous evaluation of nosocomial infections, antibiotic prescription and microbial resistance patterns.
Participating in the Swedish Intensive Care Register.
Participating in the Swedish Strategic Programme against Antibiotic Resistance.

**Research**
Research in the field of nosocomial infections.

ICU: Intensive care unit

Table 6: Annual nosocomial infection rates on the Jönköping intensive care unit

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>ICU patients (n)</td>
<td>542</td>
<td>535</td>
<td>459</td>
<td>500</td>
<td>506</td>
<td>489</td>
<td>510</td>
<td>496</td>
<td>530</td>
<td>517</td>
<td>571</td>
<td>554</td>
</tr>
<tr>
<td>VAP (n)</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>CRI/CRBSI (n)</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cl. difficile (n)</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td></td>
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</tbody>
</table>

ICU: Intensive care unit
n: numbers
VAP: Ventilator-associated pneumonia
CRI: Catheter-related infection
CRBSI: Catheter-related bloodstream infection
Cl: Clostridium
Central venous catheter insertion and care in Jönköping

A CVC team, including two anaesthesiologists and one ICU nurse, are responsible for all written documents concerning CVC and AC insertion, care and removal at the hospital. These instructions are distributed to all units using these catheters and are also available on the hospital's intranet. All anaesthesiologists are trained under supervision to perform CVC and AC insertion according to the written documents. All ICU nurses are trained at the start of their employment and thereafter every second year to assure a high adherence to these routines. The CVC team also has a network for education and the team or a trained anaesthesiologist is available around the clock for problem solution on all hospital wards and outpatient departments. Since 2006 there have been monthly measurements of adherence to basic hygiene routines throughout the hospital.

The quality control of CVC infections throughout the hospital includes continuous tip culture analysis of all CVCs removed.

This quality improvement programme developed into a scientific project resulting in this thesis.
THE AIMS OF THE STUDIES IN THIS THESIS

- To study the incidence of colonisation and infections related to central venous catheters, after implementation of evidence-based routines throughout our hospital (Study 1).

- To study the incidence of colonisation and infections related to arterial catheters, after implementation of evidence-based routines on our intensive care unit (Study 2).

- To study the long-term effects and endurance, after implementation of evidence-based routines throughout our hospital of evidence-based CVC routines, assessed as temporal variations in central venous catheters colonisation and infections. (Study 4).

- To study microorganisms responsible for colonisation and infections related to central venous catheters and arterial catheters. (Studies 1, 2 and 4)

- To identify possible risk factors for central venous catheter and arterial catheter microbial colonisation and infections (Studies 1, 2 and 4)

- To study possible transmission of Candida spp. between patients on an intensive care unit (Study 3).
MATERIAL AND METHODS

SETTING

Jönköping hospital is a 500-bed public hospital supporting most medical and surgical specialties, except thoracic and neuro surgery. The number of operations performed per year is approximately 12,000. The ICU has resources for seven patients (two single rooms, one double room and one four-bedded room) and admits around 500 patients a year. The nurse: patient ratio is 1.3:1 and the median Apache II score is 18.

STUDY DESIGN

All studies were prospective observational cohort studies.

Inclusion criteria:

Study 1. All patients ≥18 years with a CVC inserted at our hospital between September 2001 and December 2002.

Study 2. All patients ≥18 years with an AC inserted on our ICU between March 2006 and April 2008.

Study 3. All patients on our ICU with a positive Candida culture, between January 2007 and July 2008, were included. Patients who had a blood culture isolate of *C. albicans* or *C. glabrata* isolated between 2006 and 2008 in our county but not treated on our ICU were chosen as reference group.

Study 4. All patients, excluding neonates, with a CVC removed at our hospital, regardless of insertion hospital, between 2004 and 2009 were included.

Patients with subcutaneous venous ports, PICCs and CVCs inserted using cut-down technique were not included in Studies 1, 2 and 4.

All clinical and microbiological data were collected manually from patient records by the author, according to predefined study protocols.

The numbers of patients and catheters included in each study are presented in Table 7.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number of catheters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>354</td>
<td>495</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td>482</td>
<td>600</td>
</tr>
<tr>
<td><strong>Study 3</strong></td>
<td>77</td>
<td></td>
</tr>
<tr>
<td><strong>Study 4</strong></td>
<td>1674</td>
<td>2045</td>
</tr>
</tbody>
</table>
CATHETER INSERTION AND CARE

The CVCs were inserted by an anaesthesiologist using maximal sterile precautions (cap, mask, gown, gloves and large drape) and the Seldinger technique was used. ACs were also inserted by an anaesthesiologist, wearing ordinary hospital clothing and sterile gloves. Ultrasound-guided insertion was introduced during Study 4. The short-term multi-lumen CVCs inserted in Jönköping during Study 4 were all impregnated with chlorhexidine/silver-sulfadiazine. All other catheters were non-antimicrobial. The insertion site was treated with SCHA and allowed to dry for one to two minutes prior to insertion. No prophylactic antibiotics were given. All CVCs and the ACs inserted in the femoral vein were secured with monofilament sutures and the other ACs were secured with sterile adhesive stripes. After the procedure the insertion sites was covered with a semi-permeable dressing. The CVC and AC insertion was documented in the patient records after completed procedure, and registered in a database. In Studies 1 and 2, insertion documentation was also registered in study protocols.

T-CVC sutures were removed when the subcutaneous cuff had firmly healed and no semi-permeable dressings were used thereafter. Every third day (every seventh day for outpatients), dressing, stopcocks, pressure sets and injection membranes were changed, and the insertion site was treated with SCHA. Heparin flushing and locks were not routinely used, except for patients on haemodialysis outside the ICU. The CVCs were flushed four times after every infusion with ten millilitres of saline to prevent occlusion. Closed sampling pressure sets were not used for the ACs. Resting CVCs (> 24 hours) were not routinely flushed. Lipid solutions were administrated via a separate lumen when using multi-lumen catheters. All CVCs and ACs were supposed to be cultured on removal.

DEFINITIONS

CVC or AC colonisation

Studies 1 and 2: positive tip culture with ≥1 CFU without clinical symptoms
Study 4: positive tip culture with ≥1 CFU regardless of clinical symptoms
Both definitions were compared with a commonly used definition ≥15 CFU.

CRI (both CVC and AC)

Positive tip culture from a patient having at least two SIRS symptoms at CVC or AC removal, and no other obvious source of infection.

CRBSI (both CVC and AC)

Isolation of indistinguishable microorganisms from the tip culture and a blood culture sample drawn from another vessel (within 48 hours prior to or after CVC or AC removal). Isolates were regarded as indistinguishable if they shared the same phenotype and antibiogram.

Duration of catheterisation

The number of days from insertion to removal of the CVC or AC.

ICU-CVCs

All CVCs that were used to some extent on the ICU were regarded as ICU catheters.

Candida infection (Study 3)

Candida growth with clinical symptoms related to Candida spp. as judged by the attending ICU physician in consultation with the daily visiting infectious disease specialist.
MICROBIOLOGY

CVC and AC tip culture (Studies 1-4)

The catheters were removed after site treatment with SCHA that was allowed to dry. The distal 3-5 cm of the catheter tip was cut off with sterile scissors and deposited in a sterile container and cultured using a semi-quantitative standardised roll plate method. The tip culture result was considered positive if ≥1 CFU were found. The catheter tips were all cultured within 18 hours after removal.

Blood cultures (Studies 1-4)

Blood cultures were performed when clinically indicated by aspirating blood from another vessel. The bottles were incubated ≤6 days using an automated blood culture system (BAC/ALERT, bioMérieux, Inc, Durham, NC). Isolates were identified using standard methods at the local microbiology laboratory. Antibiotic susceptibility tests were performed according to Swedish standards (www.srga.org).

Candida culture and analysis (Study 3)

Surveillance cultures (tracheal secretion, catheter urine, perineal swab, wounds and incision sites) were collected every Monday from all patients with an ICU stay longer than 72 hours. Directed cultures were collected at the request of the physician responsible or the daily visiting infectious disease specialist.

Candida samples were cultured on BBL™ CHROMagar™ Candida medium (bioMérieux), and incubated at 35 °C overnight. Species determination of Candida isolates was performed on the VITEK2 compact, using the YST-card, according to the manufacturer’s recommendation (bioMérieux). Extraction and purification of DNA was performed using the Ultra Clean™ Microbial DNA Isolation Kit (MO BIO Laboratories, Inc. Carlsbad, CA) in accordance with the manufacturer’s instructions for fungi, with the following modifications: after addition of the MD1™-solution the samples were incubated at 80 °C for 30 minutes and after 45 minutes of bead beating, the samples were centrifuged for two minutes. The isolates from blood cultures were also incubated with 15 units of Zymolyase (Zymo Research, Irvine, CA) at 37 °C for 30 minutes prior to the addition of the MD1™-solution. DNA samples were amplified using the Candida fingerprinting kit according to the manufacturer’s instructions (bioMérieux). The fragments were separated using an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Finally, web-based software (DiversiLab v3.4) was used to analyse the genotypic similarity of isolates, by the Kullback-Leibler method. An internal positive control was chosen based on the number and distribution of produced fragments. Repeated analysis of the internal positive control gave an inter-run similarity of 97%. The limit for indistinguishable isolates, and thus our definition of a genotype was therefore set at 97% similarity instead of the recommended 95% (bioMérieux).
STATISTICS

Associations and differences between groups were assessed using \( \chi^2 \)-test, Fisher’s exact test, Student’s t-test or Mann-Whitney test as appropriate. The correlations between different incidences were evaluated with Spearman’s rank correlation test. Variations of variables over time were analysed with linear regression analysis.

Univariate logistic regression analyses were performed to estimate the risk for colonisation, CRI and CRBSI (Studies 1, 2 and 4). Multiple logistic regression models, controlling for catheterisation time with following stepwise introduction of significant risk factors, were performed (Studies 1, 2, and 4).

In Study 3, possible clustering of genotypes was evaluated by two analyses. Firstly; temporal clustering of individuals carrying the same genotypes using a method analogous to the spatio-temporal cluster method described by Knox\(^{125}\). We analysed the interaction between presence of specific genotypes and time instead of space and time, by cross classification of all the possible pairs of patients according to whether they harboured the same genotype or not in relation to time. A time window of 3, 7, 10, 14 and 21 days between the dates of the first positive culture was used for defining closeness in time. The inference of the observed versus the expected number of pairs was made assuming a Poisson-distribution. Secondly; which only included the most frequent genotype, a goodness-of-fit comparison between Poisson regression and negative binomial regression was intended to statistically test for temporal clustering. The outcome measure was defined as the maximum number of days between ICU stays (3, 7, 10 or 14 days)\(^{126}\).

The discriminatory power of Diversilab for \textit{C. albicans} was assessed using Simpson’s index of diversity (Study 3)\(^{129}\).

In Study 4 variations of incidences over time were analysed with statistical process control methods\(^{130}\). Seldom occurring events (CRI and CRBSI) were analysed with G-charts, evaluating the number of CVCs removed between each infection episode. Frequently occurring events (colonisation) were analysed with I-charts, evaluating quarterly incidences of colonisation. Special causes of variation were defined as a run of eight or more points on one side on the central line, one point outside the upper or lower control limit, or a run of six or more points all trending up or down.

ETHICS

All studies were approved by the Regional Ethics Review Board in Linköping.
RESULTS

CENTRAL VENOUS CATHETERS

Six hundred and five CVCs in 456 patients were included in Study 1. Complete data were obtained on 495 (82%) CVCs in 354 patients (Table 8). The reasons for the drop-outs were: missed culture 74, transfer to other hospital 16, accidental removal 14, still in use 3, and incomplete patient-records 2. The median duration of catheterisation was 7.5 days (range 0.5-407 days). The total number of patient days with a CVC in place was 9010 days.

Two thousand and fifty-three CVCs in 1682 patients were included in Study 4. This represented 74% of all CVCs used in the hospital. Complete data were obtained on 2045 CVCs in 1674 patients, since insertion date was not found for eight CVCs (Table 8). The median duration of catheterisation was 8 days (range 0-1617 days). The total number of patient days with a CVC in place was 45,026 days.

Study 4 showed a continuous increase in the number of CVCs used each year from 269 to 424 (logistic regression; adjusted $r^2=0.95$, $b=33.6$, $p=0.001$). There was also an increase in the use of the internal jugular vein from 31% of all CVCs to 58% (logistic regression; adjusted $r^2=0.90$, $b=6.0$, $p=0.003$) and a decrease in the use of the subclavian vein, from 49% to 22% (logistic regression; adjusted $r^2=0.91$, $b=-5.9$, $p=0.002$) over the study period (Table 8). There were no other trends detected over time concerning patient and CVC characteristics.
Table 8: Comparison between Study 1 and the annual numbers of central venous catheters, incidences for colonisation and infections in Study 4.

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 months</td>
<td>2004</td>
</tr>
<tr>
<td>CVCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All(^a)</td>
<td>495</td>
<td>267</td>
</tr>
<tr>
<td>ICU</td>
<td>350</td>
<td>203</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>145</td>
<td>64</td>
</tr>
<tr>
<td>Haemodialysis(^b)</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>Vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavian vein, n ((^c))</td>
<td>314(63)</td>
<td>130(49)</td>
</tr>
<tr>
<td>Jugular vein, n ((^c))</td>
<td>161(33)</td>
<td>83(31)</td>
</tr>
<tr>
<td>Femoral vein, n ((^c))</td>
<td>12(2.4)</td>
<td>39(15)</td>
</tr>
<tr>
<td>Colonisation(^d, e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All(^i)</td>
<td>7.5</td>
<td>7.2</td>
</tr>
<tr>
<td>ICU</td>
<td>13.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>4.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Haemodialysis(^b)</td>
<td>7.4</td>
<td>2.3</td>
</tr>
<tr>
<td>CRI(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All(^i)</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>ICU</td>
<td>3.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Haemodialysis(^b)</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>CRBSI(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All(^i)</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>ICU</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemodialysis(^b)</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^a\) All CVCs in the study  
\(^b\) Haemodialysis outside the ICU  
\(^c\) Percentage of all CVCs  
\(^d\) Colonisation independent of systemic symptoms  
\(^e\) Per 1000 CVC-days  
\(^f\) Study period: September 2001-December 2002

CVC: Central venous catheter  
ICU: Intensive care unit  
CRI: Catheter-related infection  
CRBSI: Catheter-related bloodstream infection
Colonisation
Sixty-nine (14%) of all CVCs showed microbial growth in Study 1. The corresponding number in Study 4 was 314 (15%). This represented an incidence of 7.7 and 7.0 per 1000 CVC-days, respectively.

In Study 4 was there a significant correlation between the quarterly colonisation incidences defined as ≥1 CFU as compared to ≥15 CFU (ρ=0.89, p<0.05) (Figure 5).

The predominant species responsible for colonisation in both studies was CoNS, followed by *Candida* spp. and *S. aureus* (Table 9). We found no isolates with vancomycin-resistant enterococci or methicillin-resistant *S. aureus*.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Study 1 (%)</th>
<th>Study 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>60</td>
<td>63.8</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>8.8</td>
<td>7.9</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>6.3</td>
<td>7.5</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>5.0</td>
<td>1.1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>2.5</td>
<td>5.8</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Others</td>
<td>7.4</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Percentage of all microorganisms found in Studies 1 and 4, respectively.*

Spp: species

CRI and CRBSI
Fourteen (2.8%) and four (0.8%) patients were classified as having CRI and CRBSI respectively, in Study 1. The incidence of CRI was 1.6 and of CRBSI 0.4 per 1000 CVC-days. Fifty-two (2.5%) and 29 (1.5%) patients were classified as having a CRI and CRBSI, respectively in Study 4. The incidence of CRI was 1.2 and of CRBSI 0.6 per 1000 CVC-days, respectively. The incidences of CRI and CRBSI over time for all patients and different subgroups are presented in Table 8.

There was a significant correlation between the quarterly incidences of CRI and CRBSI (ρ=0.83, p<0.05) in Study 4. However, there were no significant correlations between the quarterly incidences of colonisation, using either of the definitions, and CRI or CRBSI (Figure 5).
Figure 5: Quarterly incidences of central venous catheter colonisation, catheter-related infection and catheter-related bloodstream infection in Study 4.

Blood cultures in relation to CRI are shown in Table 10. Antibiotics on CVC removal was analysed in Study 4. Eight of the patients with CRI had a negative blood culture of whom seven were on antibiotics. In three patients the microorganisms, found on tip culture, were sensitive to the drug used. In 21 of the 29 cases of CRBSI, the patients were receiving antimicrobial drugs at removal of the CVC and in twelve of these the microorganisms were sensitive to the antimicrobial drug. Two cases of CRBSI were not classified as CRI in Study 4 since documentation of SIRS symptoms was missing.

All patients with a CRI or a CRBSI in Studies 1 and 4 were successfully treated with antimicrobial drugs.

The microorganism isolated on tip culture from the catheters responsible for CRI or CRBSI are presented in Table 11.

The median catheterisation time to CRI/CRBSI was 14.5 (range: 3-339) days in Study 1 and 14 days (range: 1-645) in Study 4. All cases of CRI/CRBSI with Candida spp. were diagnosed before Day 16 in Study 1. There was no significant difference in catheterisation time for CRI/CRBSI caused by bacteria or Candida in Study 4, with a median catheterisation time of 14 days (range: 3-645) and 13 days (range 1-30), respectively.
Table 10: Blood cultures in relation to catheter-related infection.

<table>
<thead>
<tr>
<th></th>
<th>CRI (n)</th>
<th>Positive blood culture (n)</th>
<th>Negative blood culture (n)</th>
<th>Blood culture not performed (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>14</td>
<td>4</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Study 4</td>
<td>52</td>
<td>27</td>
<td>8^a</td>
<td>17</td>
</tr>
</tbody>
</table>

^Seven patients were on antibiotics

CRI: Catheter-related infection  
n: numbers

Table 11: Microorganisms isolated from tip cultures and blood culture on all cases of catheter-related infection and catheter-related bloodstream infection in Study 1 (14 patients) and Study 4 (54 patients).

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of isolates found</td>
<td>Number of isolates found</td>
</tr>
<tr>
<td></td>
<td>on tip culture(%) in blood</td>
<td>on tip culture(%) in blood</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>3 (20)</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>4 (27)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3 (20)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>6 (9)</td>
<td>1^b</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>2 (13)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>1 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Diphtheroid rods</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Morganella morgagni</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Stenothrophomonas maltophilia</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Burkholderia spp.</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Achromobacter spp.</td>
<td>1 (1)</td>
<td>1</td>
</tr>
</tbody>
</table>

^Percentage of all positive cultures responsible for catheter-related infection and catheter-related bloodstream infection in Studies 1 and 4, respectively.

^One patient had a positive blood culture with both Staphylococcus aureus and Enterococcus faecalis. The same isolates were found on the simultaneously performed tip culture.

n: numbers
Statistical Process Control (Study 4)
There were no occasions were the variations in incidence for colonisation was higher or lower than expected by natural (common cause) variation. However, analysis for CRI and CRBSI revealed two occasions were the number of CVCs removed between each CRI and CRBSI were higher than expected, which indicated a period with lower infection rates than expected. Six measurements of CRBSI revealed a continuous downward run indicating a period of poorer performance (Figure 6).

Figure 6: Statistical process control: Geometric charts representing the number of central venous catheters removed between each episode of catheter-related infection and catheter-related bloodstream infection in Study 4. Lined circles represents four periods of low infection rates not explained by natural variation. Dotted ovals represents a period with increasing infection rate not explained by natural variation.

CVC: Central venous catheter
CRI: Catheter-related infection
CRBSI: Catheter-related bloodstream infection
Risk factors
Univariate analysis revealed that catheterisation time was a significant risk factor for both colonisation (odds ratio: 1.011 per day (95% CI: 1.004-1.017)) and CRI (odds ratio: 1.009 per day(95% CI: 1.003-1.015) in Study 1 but only for CRI (odds ratio: 1.002 per day (95% CI: 1.000-1.004)) in Study 4. Multivariate analysis revealed that chronic haemodialysis was the only risk factor for colonisation (OR: 4.4 (95% CI: 2.0-9.8) in Study 1 and no risk factors were found for CRI or CRBSI. Risk factor analyses for Study 4 are shown in Table 12.

Table 12: Risk factor analyses in Study 4 controlling for catheterisation time using multiple logistic regression for central venous catheter colonisation, catheter-related infection and catheter-related bloodstream infection.

<table>
<thead>
<tr>
<th></th>
<th>Colonisation OR (95% CI)</th>
<th>CRI OR (95% CI)</th>
<th>CRBSI OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Apache II score</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Non-ICU use</td>
<td>1.33 (1.03-1.74), p=0.029*</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>ns</td>
<td>2.79 (1.01-7.69), p=0.048</td>
<td>4.47 (1.34-4.89), p=0.015</td>
</tr>
<tr>
<td>Multi lumen CVC</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Insertion Hospital</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mortality</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>IJV compared to SV</td>
<td>2.41 (1.75-3.33), p=0.0001</td>
<td>2.61 (1.19-5.68), p=0.016</td>
<td>ns</td>
</tr>
<tr>
<td>FV compared to IJV and SV</td>
<td>1.39 (1.02-1.89), p=0.035</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No antibiotics on removal</td>
<td>1.65 (1.26-2.13), p&lt;0.0001</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Not statistically significant when haemodialysis or antibiotics were controlled for.

OR: Odds ratio
CI: Confidence interval
IJV: Internal jugular vein
SV: Subclavian vein
FV: Femoral Vein
ns: not statistically significant
ARTERIAL CATHETERS

Six hundred and ninety-one ACs were inserted in 539 patients. Complete data were obtained on 600 (87%) catheters in 482 patients. The median duration of catheterisation was 2 days (range: 0.5-38 days). The total number of patient days with an AC in place was 2567 days.

Twenty catheters exhibited microbial growth, of which four had two different isolates. The incidence of colonisation was 7.8 per 1000 catheter-days. The microorganisms identified were 22 CoNS, 1 C. albicans and 1 Klebsiella pneumoniae. Eighteen of these were radial artery- and two were femoral artery catheters.

Five of the catheters were associated with AC-CRI. The incidence of AC-CRI was 2.0 per 1000 catheter-days. Tip culture revealed that three of these catheters had < 15 CFU. Two of these three catheters were removed while the patient already had suitable antibiotic treatment. None of the patients were treated with antibiotics when the two catheters with ≥15 CFU were removed. The only microorganism responsible for AC-CRI was CoNS. In all five cases the AC was inserted in the radial artery.

Only one of the five patients with AC-CRI had a blood culture performed and this was negative. The patient was given vancomycin prior to culture. We found no cases of AC-CRBSI.

Three hundred and ninety-three patients (73%) had a simultaneous AC and CVC. Seventeen of the 20 patients with AC colonisation had simultaneous CVC, and in six of the 17 patients tip cultures revealed indistinguishable isolates on the AC and CVC. There was a total of ten CVC-CRI and in four of these patients AC tip culture showed indistinguishable isolates. According to definition they both had an AC-CRI and a CVC-CRI.

Significant risk factors for AC-colonisation and AC-CRI are shown in Table 13.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>AC-colonisation</th>
<th>AC-CRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonisation of a simultaneous CVC</td>
<td>104.5 (18.7-584.7)*</td>
<td>384.0 (34.7-4244.0)*</td>
</tr>
<tr>
<td>CRI on a simultaneous CVC</td>
<td>20.6 (5.0-85.8)*</td>
<td>253.8 (22.1-2518.0)*</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td>7.3 (1.0-52.9)</td>
</tr>
</tbody>
</table>

* p<0.0001
* p=0.048

AC: Arterial catheter
OR: Odds ratio
CI: Confidence interval
CVC: Central venous catheter
CRI: Catheter-related infection

Table 13: Risk factors for arterial catheter-colonisation and arterial catheter-related infection.
CANDIDA TRANSMISSION

During the study period 714 patients were treated on 792 occasions on our ICU. A microbiological culture was performed in 679 (86%) of the ICU stays. Candida spp. were isolated from 77 patients with 78 ICU stays. Hence, patients harboured Candida spp. in twelve per cent of ICU stays in which a culture was performed. Seventy-five per cent of the patients had a negative candida culture within a week prior to the first positive culture. Clinical data and comparison between patients with negative and positive Candida cultures are shown in Table 14.

Table 14: Baseline characteristics of four groups of intensive care unit patients according to Candida spp. findings.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Comparison</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with neg Candida culture</td>
<td>Patients with pos Candida culture</td>
<td>Group 1 and 2</td>
<td>Patients with Candida colonisation</td>
<td>Patients with Candida infection</td>
<td>Group 3 and 4</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>625</td>
<td>77</td>
<td>65</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ICU stays (n)</td>
<td>679</td>
<td>78</td>
<td>66</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (0-90)</td>
<td>69 (17-89)</td>
<td>p=0.0012</td>
<td>70 (17-89)</td>
<td>72 (54-79)</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>58/42</td>
<td>50/50</td>
<td>ns</td>
<td>42/58</td>
<td>67/33</td>
</tr>
<tr>
<td>Apache II score</td>
<td>18 (0-48)</td>
<td>24.5 (11-41)</td>
<td>p&lt;0.0001</td>
<td>24 (11-41)</td>
<td>27 (21-30)</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>1 (0.1-56)</td>
<td>14 (1-56)</td>
<td>p&lt;0.0001</td>
<td>12 (1.56)</td>
<td>18 (14-43)</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>9</td>
<td>10</td>
<td>ns</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>22</td>
<td>41</td>
<td>p&lt;0.0001</td>
<td>36</td>
<td>58</td>
</tr>
</tbody>
</table>

*χ² or Student’s t-test
*bFishers’ test or Student’s t-test
neg: negative
pos: positive
n: numbers
ICU= intensive care unit
ns= not statistically significant
Antibacterial drugs were prescribed within seven days prior to the first positive Candida culture in 74 (95%) cases. The median number of different antibacterial drugs given to each patient within this period was 3 (range: 0-5). Antifungal therapy was administered to 32 (41%) patients, 22 before and ten after the result of the fungal culture was known. Twelve (15%) of the patients harbouring Candida spp. were judged to have one or more clinical Candida infections. Clinical data and comparison between patients with Candida infection and those with Candida colonisation are shown in Table 14. Candida spp. contributed to mortality in two cases.

Cultures and genotypes
A total of 180 isolates were found on the ICU of which 81% and 19% were obtained from surveillance and directed cultures, respectively. The Candida spp. found were: C. albicans (129), C. glabrata (36), C. krusei (6), C. parapsilosis (4), C. dubliniensis (4) and C. sphaerica (1).

DiversiLab analysis revealed 27 C. albicans genotypes (Ca1 to Ca27) in 55 patients and ten C. glabrata genotypes (Cg1 to Cg10) in 16 patients. The other species were excluded from molecular analysis due to the few isolates found. The diversity index for C. albicans by Simpson index of DiversiLab was 0.94. The median number of patients for each C. albicans genotype were 2 (range: 1-19) and the three most disseminated genotypes were Ca8 (19 patients), Ca11 (ten patients) and Ca12 (eight patients) (Figure 7). Five C. glabrata genotypes were found in more than one patient and Cg3 was the most disseminated (five patients) (Figure 7). There was no difference in the distribution of genotypes between patients colonised and infected with C. albicans within the ICU.

Possible clustering, indicated by overlapping ICU stays of patients with indistinguishable genotypes, was observed on seven occasions with C. albicans and on two occasions with C. glabrata (Figure 7). Genotypes Ca8 and Ca11 represented six of these possible clusters (Figure 8).

No overlapping was seen for the frequent genotypes Ca12 or Cg3. By using the modified spatio-temporal cluster analysis, we found a non-significantly increased number of pairs at intervals of 3, 7, 10 and 14 days. At a 21 day-interval clustering was observed (Observed/Expected-ratio=1.42, p=0.016). The other cluster analysis could not be performed due to limited sample size.

There were no differences between patients in the reference group and the ICU patients with positive Candida culture as regards age, gender, surgery and antibiotic treatment. Analysis of isolates from the reference group revealed 24 C. albicans genotypes in 21 patients, and eight C. glabrata genotypes in ten patients. Three C. albicans genotypes were found in both the ICU and reference groups. None of these genotypes had a temporal occurrence in the ICU indicating transmission. The most frequently isolated C. albicans genotypes in the ICU group (Ca8 in 19 patients and Ca11 in ten patients) were not found in the reference group (p=0.004 and p=0.03). Fourteen C. albicans genotypes were found in more than one patient in the ICU group and three in the reference group (p=0.0013).

No identical C. glabrata genotypes were found in both the ICU and the reference group (not significant).
Figure 7: Patient distribution per genotype. Overlapping of intensive care unit stays for patients with the same genotype is shown by bold borders.

| Genotype | Ca1 | Ca2 | Ca3 | Ca4 | Ca5 | Ca6 | Ca7 | Ca8 | Ca9 | Ca10 | Ca11 | Ca12 | Ca13 | Ca14 | Ca15 | Ca16 | Ca17 | Ca18 | Ca19 | Ca20 | Ca21 | Ca22 | Ca23 | Ca24 | Ca25 | Ca26 | Ca27 | Cg1 | Cg2 | Cg3 | Cg4 | Cg5 | Cg6 | Cg7 | Cg8 | Cg9 | Cg10 |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

Number of patients per genotype:

1 1 2 3 5 1 1 19 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1

Number of overlapping intensive care unit stays per genotype:

1 4 2 1
Figure 8: Intensive care unit stay for patients harbouring genotype Ca8 (dark boxes) and C11 (light boxes) over the study period.

Ca = Candida albicans
P = Patient
DISCUSSION

CVCs are necessary in modern healthcare but infections related to these catheters contribute to significant morbidity, mortality and healthcare costs. In this thesis, we report continuously low annual incidences of CRI/CRBSI in both short- (16 months) and long-term (six years) follow-up studies after implementation of evidence-based hygiene routines for CVC insertion and care at our hospital. We did not observe any mortality caused by CVC infections. We believe that our results are due to high awareness of CVC infections and high adherence to evidence-based hygiene routines throughout our hospital.

Our routines for insertion and care are based on previous recommendations from the CDC. These recommendations have been evaluated in previous studies by others, but never in Scandinavia. The hospital’s CVC team, available for education and support in the care of patients with a CVC, is now well-established. The team or a trained anaesthesiologist is available for support around the clock. The team arranges practical and theoretical education sessions on a regular basis for the ICU staff and on demand for personnel on other units. The team has a continuous surveillance system for the entire hospital, in that all CVCs removed should have their tips cultured. All departments receive annual reports on colonisation rate and microorganisms for their unit compared to the hospital as a whole.

We have used the incidence rates of three different indicators of infectious complications related to the use of a CVCs and ACs; colonisation, CRI and CRBSI. Most studies have used quantitative or semi-quantitative methods to demonstrate colonisation. We used a more sensitive definition (≥1 CFU) than the commonly used (≥15 CFU) since several factors such as antimicrobial CVCs, antimicrobial treatment, removal technique, and time from removal to culture, may influence the culture results. We compared our data using cut-off values ≥1 CFU with ≥15 CFU and found a significant correlation between these two measurements. Furthermore, data on the cut-off values for different microorganisms in relation to the semi-quantitative culture techniques are limited. In Study 1 colonisation was defined as microbial growth on tip culture in the absence of SIRS-symptoms and in Study 4 as microbial growth regardless of SIRS-symptoms. The reason for this shift is that in Study 4 we looked to see if tip culture alone could be used as a surrogate-marker for CRI or CRBSI. Furthermore, this definition is more in consistency with international recommendations (www.ecdc.europe.eu).

The reason for studying colonisation is that it provides a picture of possible microorganisms involved, including their resistance patterns, thus providing guidance when treating CVC infections. The culture procedure and presence of microorganisms on cultured catheter tips is itself a reminder, serving to increase clinical awareness of the risk of a CVC infection. A positive tip culture is a prerequisite for a diagnosis of CRI. A large proportion of all patients, especially on the ICU, have SIRS symptoms on CVC removal due to different causes. The catheter has to be evaluated as one origin of the SIRS symptoms. These three factors justify, in our opinion, the routine of CVC tip culture for all CVCs removed. However, we could not verify previous findings that colonisation may be used as a surrogate indicator of CRI or CRBSI.

Most studies have used CRBSI as an endpoint for severe infections where the entry of the causative microorganism is the CVC. CRBSI is well-defined and suitable for research if a high degree of blood cultures is secured in patient with a CVC and SIRS symptoms. However CRBSI, in our opinion, is too narrow a definition since it requires...
positive blood cultures and thus has several limitations; cultures not always performed, antimicrobial treatment preventing growth of microorganisms, intermittent release of microorganism to the blood, inappropriate transportation or delay in coming to the laboratory. The paired blood culture test, which is mandatory for diagnosing CRBSI, with a catheter in situ is also problematic in severely ill patients on the ICU. These patients tend to have several different intravascular catheters at the same time (i.e. 4-lumen CVC, haemodialysis-CVC, pulmonary artery catheter with an introducer-CVC, and arterial catheter. Blood cultures must be taken from all lumen repeatedly, resulting in a considerable amount of blood taken from a severely ill patient.

We consider CRI, to be the most valuable clinical measurement as it captures all patients with SIRS symptoms who have microorganisms on their CVC, shown by positive tip culture. Recent European studies have used a CRI definition similar to ours. One difficulty with the CRI definition is that the CVC must be removed for culture. Another difficulty is that most patients having SIRS symptoms and a CVC in place have their symptoms from causes other than a CRI. This means that several catheters will be removed for culture without being the source of the patient’s symptoms. However, in clinical practice these patients must be evaluated by the physician responsible who must decide which action shall be taken. Depending on several factors such as underlying disease, immune status, clinical symptoms, type of catheter, possible microorganisms, coagulation status, available veins and the need for the catheter, the decision must include individualised considerations of whether the catheter should be removed or not, correct cultures, and the implementation or not of antimicrobial therapy.

Many reports have used CRBSI incidences as an indicator of quality of care of patients with a CVC. CRBSI incidences reported by others, from both ICU and non-ICU settings vary from zero to ten per 1000 CVC-days. Rates below 2 per 1000 CVC-days are difficult to achieve on an ICU under long periods. Our CRBSI incidence was 0.4 and 0.6 per 1000 CVC-days in Study 1 and 4. The corresponding incidences on the ICU were 1.9 and 1.4 per 1000 CVC-days, respectively. However, the incidences of CRI for all CVCs were higher (Study 1: 1.6, Study 2: 1.2 per 1000 CVC-days) compared to CRBSI. The discrepancy between the incidences of CRI and CRBSI has also been reported by others. Thus, in the clinical setting, we prefer recording the incidence of CRI as an indicator of the quality of CVC care since it reflects a larger proportion of the patients with CVC infection than does CRBSI.

Several studies, mainly from ICUs, have shown that the implementation of simple CVC routines is successful in decreasing the incidence of CRBSI to a very low level. We have found only three studies evaluating the long-term effect of an intervention. All these studies indicate that the implementation of evidence-based routines is successful over a long period of time. There is no study, to our knowledge, running over such a long period of time as our continuous six year follow-up investigation. Our results also indicate that it is possible to achieve low rates of infection over a long period of time. Quarterly registration of incidences of colonisation, CRI and CRBSI showed greater variations compared to annual incidences. Hence, in our setting quarterly CRI/CRBSI rates are preferable as quality indicators since these and statistical process control methods can identify periods of insufficient CVC care.

Statistical process control, adopted from the technical industry, has been used in several medical studies. To our knowledge only one study has used SPC for analysing CRBSI.
Our study design made it possible to analyse variations in the incidence rates of colonisation, CRI and CRBSI by using statistical process control, over time. Although the incidences of CVC colonisation and infection varied during the study period we could only identify one period in which an increased rate of CRBSI could not be explained by natural (common cause) variation. Natural variation, as shown by statistical process control, highlights the importance of continuous measurements and efforts to reduce the incidence of CVC infections. Hence, point prevalence and evaluations over short periods of time could provide erroneous information on the incidences of CVC colonisation and CRI/CRBSI.

Risk factor analysis should be regarded with caution, since confounding factors are difficult to fully control for. Several studies have shown that catheterisation time is an important risk factor for CRI and CRBSI and the removal of a CVC that is no longer required is a cornerstone in CRBSI prevention\(^\text{10,32}\)(www.sfai.se, www.sbu.se). We found in Studies 1 and 4 that catheterisation time was a weak risk factor for CRI and not a risk for CRBSI. We believe that the explanation for catheterisation time not being a significant risk factor for CRBSI is the continuously high adherence to hygiene routines, including the removal of CVCs no longer required.

We have also found that the jugular vein is associated with a higher CRI incidence as compared to the subclavian vein. This is in accordance with other studies, none of which has been PRCT\(^\text{135}\). The insertion of CVCs in the femoral vein is controversial as regards CVC infections. We could only verify this vein as a risk factor for colonisation. This could reflect the few femoral catheters used (16%). We have preferably used the femoral vein on the ICU in situations where coagulopathy is a problem, thereby decreasing the risk for severe bleeding complications. Other studies have found conflicting results, but the only PRCT comparing the femoral and then internal jugular vein on an ICU found no difference in infectious complications\(^\text{136}\). In Study 1 only patients on chronic haemodialysis showed increased risk for CRI. The risk for CRI and CRBSI is increased for all patients on haemodialysis in Study 4, which is in accordance with other studies. However, chronic haemodialysis was not a risk factor for CVC infection in Study 4 and the incidence of CRBSI in this group was low (0.4/1000 CVC-days). A meta-analysis revealed incidence rates of CRBSI with CVCs and t-CVCs for haemodialysis to be 4.8 and 1.6 per 1000 CVC-days, respectively.

We have found a spectrum of microorganisms responsible for colonisation and CVC-infections similar to that found by others, but the proportion of Candida spp. was high compared to others\(^\text{77 94 106 137}\). We found no vancomycin-resistant enterococci or methicillin-resistant S. aureus, which probably reflects the situation in our hospital, where the frequency of these bacteria is low. The high proportion of Candida spp. has also been found in another study evaluating CRBSI on an ICU\(^\text{98}\). Possible explanations for this could be differences between our hospital and hospitals abroad in patient case-mix, varied patient microbial flora, and antimicrobial treatment. Different microorganisms have different abilities to cause CRI/CRBSI. The species most often isolated from colonisation and CRI/CRBSI is CoNS. However, only few of the CoNS isolated on tip culture were responsible for CRI/CRBSI. The other more commonly found microorganisms such as Candida spp., S. aureus, gram negative rods, and Enterococcus spp. are much more often associated with CRI/CRBSI when they are found on tip culture. These observations must be considered when on evaluating the presence of a pathogen on tip culture.

There are limited data on the type of microorganism responsible for CVC infections in relation to catheterisation time. In our Study Candida infections were not diagnosed later than
bacterial infections, as proposed by others. This implies that anti-fungal treatment must be considered in the treatment of CVC infections, regardless of catheterisation time. There are no published Scandinavian studies on AC-related infections. The general view has been that ACs seldom cause CRI or CRBSI, although recent international studies have shown that they do so in a significant number of cases. We found a total AC-CRI rate of 2.0 per 1000 catheter-days. This is less than the CVC-CRI incidence of 3.8 and 3.0 per 1000 catheter-days that we found on our ICU in Studies 1 and 4, respectively. We found no cases of AC-CRBSI, although the incidence may be underestimated because blood cultures were not always performed and the majority of patients were on antibiotics. A meta-analysis has shown a mean AC-CRBSI incidence of 1.7 per 1000 catheter-days. The lower rate of CRI/CRBSI with ACs compared to CVCs is in agreement with most other studies. ACs may be less prone to causing CRI/CRBSI than CVCs. Possible reasons for this could be the differences in use of an AC and a CVC, oxygenation of the blood, blood flow etc. This must be further studied. We believe that adherence to hygiene routines, including AC insertion and care, is the reason for the low rate of AC infection found in this study. Most of our catheters were inserted using catheter over cannula technique. This is contrary to most other studies and may have influenced the colonisation and infection rates. However, since AC infections are a significant problem, blood-cultures exclusively drawn from the AC cannot be recommended since a positive culture will not distinguish between AC-colonisation, AC-CRI and bacteraemia from other sources. In the clinical situation where there is suspicion of CRI/CRBSI caused by an AC or CVC, a peripheral blood culture must be performed at the same time as tip cultures or blood cultures via the catheters.

There are limited data on risk factors contributing to AC-CRI. Previous studies have found that insertion via the femoral artery and catheterisation time are possible risk factors. This is also supported by a recent multi-centre study, but could not be verified in another study. We could not verify these findings, possibly because of the infrequent use of the femoral artery and the low AC-CRI incidence in our study. Multivariate analysis identified immunosuppression, CVC colonisation, and CVC-CRI as risk factors in our study. Microbial growth or coexisting infections on AC and CVC needs clinical attention. It is impossible to determine which catheter was colonised or infected first, and whether or not cross-contamination is important pathogenetically. However as CVC colonisation and CRI were risk factors for AC-CRI, we suggest that both the AC and CVC should be considered for removal if one is found to be colonised and suspected as being a source of infection.

In accordance with other studies we found that CoNS was the dominating agent for colonisation. Furthermore CoNS was the only microorganism responsible for AC-CRI. Other studies have found a more heterogeneous microbiology causing AC-CRBSI. This could reflect differences in hospital microbiological flora, patient characteristics and adherence to hygiene routines.

Transmission of pathogenic bacteria between patients on an ICU is well documented but the role of Candida spp. in this mechanism has not fully been explored and previous studies have shown conflicting results. One of the main problems with studies on Candida transmission is the selection of a representative reference group. Genotype variations within specific populations and geographical areas is poorly documented. Furthermore, ICU patients are not comparable with a normal population since they are often severely ill and exposed to antibiotics prior to their ICU stay, and this influences the microbial ecology. Thus, a reference group showing
Candida genotypes found in the local population might not be the best choice. In this study, we included blood culture isolates from severely ill patients in the same region, but not from our ICU, as a reference group, since they represent Candida isolates from a similar patient population. As a complement, we performed a temporal cluster analysis to evaluate genotype distribution with no relation to a reference.

The colonisation rate of *Candida* spp. among ICU patients varies significantly in different reports, depending on several factors such as diagnosis, type of surgery, length of ICU stay as well as selection of culture sites and sampling techniques. The colonisation rate of twelve per cent in our study is low. A possible explanation for this could be that we have included all patients regardless of length of ICU stay, and that a limited number of throat cultures were performed. This could also be explained by a high antifungal prescription rate between 2004 and 2009 compared to other Swedish ICUs (unpublished data, Swedish Institute for Communicable Disease Control) or different patient characteristics. The patients harbouring *Candida* spp. were older, had a higher Apache II score, longer ICU stay, and were more often operated on compared to other ICU patients, which is in accordance with other studies. We found only two blood cultures positive for *Candida* spp. on the ICU, of which both of which were *C. glabrata*. The proportion of patients not cultured was 14%, predominately patients with a short ICU stay and no infection. Hence, these patients presumably have a low impact on transmission.

Seventy-five per cent of the ICU patients from whom *Candida* spp. was isolated had a prior negative Candida culture. The switch from negative to positive Candida culture during an ICU stay could be the result of promoted growth of endogenous strains or of transmission.

However, certain genotypes were more frequently isolated than others among the ICU patients, and the distribution of some genotypes gave the impression of temporal clustering indicating transmission. Furthermore, two genotypes were significantly more frequently isolated from the ICU patients compared to the reference group, and genotypes found in more than one patient were significantly more often seen on the ICU. These results suggest that some genotypes may have a greater tendency to be transmitted between patients on the ICU. This is supported by the temporal cluster analysis using a time interval of 21 days after the first positive Candida culture.

The DiversiLab system has been shown to be useful for local studies on Candida epidemiology. A recent study, however concluded that DiversiLab has a moderate discriminatory power, which may lead to clustering of isolates not closely related genetically. In the present study, this could have influenced the number of accumulations and led to an overestimation of transmissions. However, the use of a standardised and easy-to-use commercially available method enables rapid tracking of isolates and may indeed have the potential to detect on-going outbreaks. Furthermore, knowledge of local Candida epidemiology may enhance the possibility to prevent nosocomial transmission, identify more virulent strains and could predict infection rates enabling optimised anti-fungal treatment and better patient outcome as a result. In cases of inconclusive discrimination a second method at a reference laboratory could be used to strengthen the clinical conclusions regarding nosocomial spread.

There are possible explanations other than transmission for the Candida genotype distribution seen in this study. Firstly, these genotypes could be more common in the general population. However, we do not think that this is a likely explanation since these genotypes were
infrequent in the reference group. Secondly, these genotypes could have been selected, as a result of antibiotic treatment. This is also unlikely since the majority of patients in the reference group had also received antibiotics. Thirdly, patients harbouring a frequently occurring genotype could be more predisposed to ICU treatment. This is contradicted by the fact that there was no difference in the distribution of these genotypes between ICU patients colonised or those infected with *Candida* spp.

Previous studies, predominately from ICUs and neonatal wards, have stated that transmission of *Candida* spp. may occur[111-114 116 117 120]. However, this has only been supported by simultaneously occurring genetically indistinguishable isolates, with a limited reference groups or cluster analysis, not including time as a variable[112 115].

Invasiveness and tendency to be transmitted are two important virulence traits of microorganisms, but these two properties are not always linked[127]. Two of the genotypes in this study may have had a greater tendency to be transmitted but we could not demonstrate increased invasiveness.

Since other studies have found indistinguishable genotypes in both healthcare workers and patients, a role of healthcare workers in transmission is likely[111 112 121]. Growth of Candida in the environment has seldom been studied and the significance of the inanimate environment as a source of *C. albicans* transmission on the ICU is not known[142].
CONCLUSIONS

- Low incidences of CVC-colonisation and CVC-infections, compared to international studies, were found in an entire hospital patient population after implementing evidence-based routines for insertion and care of CVCs.

- Low incidences of AC-colonisation and AC-infections, compared to international studies, were found after implementing evidence-based routines for insertion and care of ACs.

- Sustained low incidence rates for CVC-colonisation and CVC-infections were found in an entire hospital patient population over a six-year follow-up period after implementing evidence-based routines for insertion and care of CVCs.

- Microorganisms responsible for CVC colonisation and infections were similar to those found in international studies. However, *Candida* spp. were found more often than in most other studies. There was no difference in catheterisation time for CVCs associated with CRI/CRBSI caused by *Candida* spp. as compared to CRI/CRBSI caused by bacteria.

- Only CoNS were responsible for CRI related to ACs.

- Risk factors for CVC colonisation in Study 1 were; catheterisation time and chronic haemodialysis and in Study 4; no antibiotics on removal, use of the internal jugular vein as apposed to the subclavian vein, and of the femoral vein as apposed to the subclavian and internal jugular veins.

- Risk factors for CRI associated with CVCs were catheterisation time (Studies 1 and 4), chronic haemodialysis (Study 1), haemodialysis in general (Study 4) and CVCs inserted in the internal jugular vein compared to the subclavian vein (Study 4).

- Risk factors for AC colonisation were colonisation or CRI of a simultaneous CVC.

- Risk factors for AC-CRI were colonisation or CRI of a simultaneous CVC, and immunosuppression.

- Transmission of *Candida* spp. between ICU patients is possible.
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