# Central Venous Catheterization. Aspects of Catheter-Related Infections and Thrombosis.

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# Central Venous Catheterization

## Aspects of Catheter-Related Infections and Thrombosis

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LUND
UNIVERSITY

DOCTORAL DISSERTATION
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**Title and subtitle:** Central Venous Catheterizaton - Aspects of Catheter-Related Infections and Thrombosis

**Background:** Central venous catheters (CVCs) are associated with numerous complications, which lead to increased mortality, longer hospital stays, and higher costs. As long-term complications such as catheter-related infections (CRI) and catheter-related thrombosis (CRT) are believed to be not only interrelated but also preventable, it prompts further exploration.
**Aims:** This thesis was conducted to study: (i) the incidence of CRI in non-selected and selected cohorts (ii) measures aiming to reduce and prevent CRI (iii) risk factors associated with CRI (iiii) histopathological changes in the vein wall associated with indwelling CVCs.
**Methods:** Three retrospective and one prospective study were conducted. The first study evaluated the CRI incidence of 1,722 CVC insertions in non-selected patients, one year before and the year after implementing a simple hygiene insertion bundle. The second study explored the prevalence and incidence of CVC-related complications, including suspected CRI (sCRI), in 589 inserted CVCs in 387 high-risk hematology patients. The third study used automatic data scripts to collect data on 9,924 CVC insertions to evaluate the CRI incidence in non-selected patients approximately ten years after the implemented hygiene insertion bundle. The fourth study prospectively included 12 patients with a CVC who were subject to autopsy for further macro- and microscopic examination of the vessel with the inserted CVC.
**Results:** In the first study, the incidence of CRI was low and the implemented hygiene bundle further reduced CRI, where multi-lumen catheters were associated with an increased risk of CRI. The second study demonstrated a relatively high prevalence of mechanical complications and sCRI incidence in this selected cohort, with high body mass index and male gender being independently associated with sCRI. The third study, confirmed a sustained low incidence of CRI in a non-selected cohort, associating male gender and multi-lumen catheters with an increased risk of CRI. The fourth study demonstrated CRTs with adjacent inflammatory changes and fibrotic vessel wall thickening in all investigated cases.
**Conclusions:** The incidence of CRI in both non-selected and selected high-risk cohorts was low, and the implementation of a simple hygiene bundle seemed to play a key role in reducing CRIs. We observed that high-risk patients with hematologic malignancies had a higher risk for CRI when compared with non-selected patients. Also, we identified both well-known, as well as less known, risk factors for CRI. The utilization of automatic data scripts enabled efficient data collection, suggesting this method could be useful for future analyses of CVC-related complications. Lastly, we demonstrated that CRT with adjacent inflammatory vessel wall thickening was very common, which is worrying, as CRTs may cause life-threatening complications.

**Key words:** central venous catheters, catheter-related infections, catheter-related thrombosis, catheter-related complications

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# Central Venous Catheterization

## Aspects of Catheter-Related Infections and Thrombosis

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*To my mom*

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# List of Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Thorarinsdottir HR, **Rockholt MM**, Klarin B, Broman M, Fraenkel CJ, Kander T. Catheter-related infections: A Scandinavian observational study on the impact of a simple hygiene insertion bundle. *Acta Anaesthesiol Scand* 2020; 64(2):224–231.

II. **Rockholt MM**, Thorarinsdottir HR, Lazarevic V, Rundgren M, Kander T. Central venous catheter-related complications in hematologic patients: An observational study. *Acta Anaesthesiol Scand* 2022; 66(4):473-482.

III. **Rockholt MM**, Agrell T, Thorarinsdottir HR, Kander T. Sustained low catheter related infection (CRI) incidence in an observational follow-up study of 9,924 catheters using automated data scripts as quality assurance for central venous catheter (CVC) management. *Infect Prev Pract* 2023; 5(2):100273.

IV. **Rockholt MM**, Badri AM, Naddi L, Englund E[1], Kander T[1]. Macro- and Microscopic Changes in Veins with Short-Term Central Venous Catheters: An Observational Autopsy Study. Manuscript submitted to *Eur J Anaesthesiol,*

[1] These authors contributed equally.

# Abbreviations

| | |
|---|---|
| CFU | colony-forming unit |
| CHC | central hemodialysis catheter |
| CLABSI | central line-associated bloodstream infection |
| CRBSI | catheter-related bloodstream infection |
| CRI | catheter-related infection |
| CRT | catheter-related thrombosis |
| CVC | central venous catheter |
| ICU | intensive care unit |
| sCRI | suspected catheter-related infection |
| SIRS | systemic inflammatory response syndrome |

# Introduction

Central venous catheters (CVCs) are biomedical devices, inserted into large central veins of the body and are essential in modern healthcare [1]. The first CVC insertion was described as early as 1733, when the English clergyman Stephen Hales fixed a glass tube to the left jugular vein of a horse in order to measure venous pressure and cardiac output [2, 3]. About two centuries later, in 1929, German doctor Werner Frossman successfully inserted a ureteric catheter into his antecubital vein using fluoroscopic guidance, and thus, became the first one to ever describe central venous catheterization in humans [4].

Since then, millions of catheters have been inserted. They are indispensable tools in modern clinical practice as they provide reliable and direct access to the central circulatory system, allowing for the administration of vasoactive drugs, chemotherapy, and parenteral nutrition along with venous access for extracorporeal blood circuits, hemodynamic monitoring, and hemodialysis [1, 5]. Despite the benefits of CVCs, their use has been associated with a substantial risk of complications, including mechanical complications, infectious complications, and thrombosis [6, 7]. Long-term complications such as catheter-related infections (CRI) and catheter-related thrombosis (CRT), which are believed to be interrelated [8-12], are known to cause increased mortality, longer hospital stays, and higher costs [13, 14].

In the last decades, numerous studies assessing CVC-associated long-term complications have been presented, leading to improvements in the prevention and management of CRI and CRT [5, 15-27]. By implementing and standardizing routines, the incidence and prevalence of these complications have been significantly reduced [15, 16].

Despite evidence suggesting CRI and CRT to be largely preventable, these complications still occur [24, 28, 29], prompting further exploration.

# Central Venous Catheters

By definition, a CVC is a flexible tube inserted through a central vein with the catheter tip in the central circulation [4]. Anatomically, the tip should be placed between the cranial third of the superior vena cava and the cavo-atrial junction, or in cases of femoral insertion, the inferior vena cava [30].

These devices are mainly used in perioperative and intensive care medicine. However, they also play an important role in managing medical, surgical, pediatric, and oncological patients. Their widespread use has resulted in making it one of the most common invasive procedures, performed in approximately 3.7-8.0% of all hospitalized patients [31]. It is estimated that about five million catheters are inserted in the United States each year [32]. In the United Kingdom, the estimated figure is about 250,000 catheter insertions per year [33], and in Sweden, more than 50,000 catheterizations are inserted annually [34].

The choice of CVC depends on a variety of factors, including the expected duration (short-term, mid-term, or long-term), the required number of lumens (single- or multi-lumen), and the indication for the CVC (**Table 1**).

In contrast to the wide range of indications, the contraindications for CVC placement are usually relative and depend on the clinical situation. General contraindications include infected, burned or traumatized insertion sites, as well as thrombosis or stenosis of the target vein [35].

**Table 1.** Selection of central venous access device based on indication[1].

| Indication [4, 36] | Suggested type of catheter [37-41] |
|---|---|
| **Administration of vesicant** | |
| Electrolyte salts | Single- or multi-lumen non-tunneled CVC |
| Hyperosmolar fluids (e.g. total parenteral nutrition) | Single-lumen tunneled CVC; PICC |
| Vasoactive agents (vasopressors) | Multi-lumen non-tunneled CVC |
| Cytotoxic agents (chemotherapy) | Single-lumen tunneled CVC; Port-á-cath |
| Antibiotics | Single- or multi-lumen non-tunneled CVC |
| **Monitoring** | |
| Central venous pressure | Multi-lumen non-tunneled CVC |
| Central venous oxyhemoglobin saturation (ScvO2) | Multi-lumen non-tunneled CVC |
| Pulmonary arterial pressure | Swan-Ganz multi-lumen non-tunneled catheter |
| Temperature monitoring (catheters) | Multi-lumen non-tunneled cooling catheters |
| **Difficult peripheral intravenous access** | Single- or multi-lumen non-tunneled CVC |
| **High-volume/flow procedures** | |
| Hemodialysis and plasmapheresis | Multi-lumen tunneled or non-tunneled CHC |
| Extremely rapid fluid resuscitation | Multi-lumen non-tunneled CVC |
| **Access for extracorporeal-blood circuits** | Two single-lumen or bi-caval dual-lumen non-tunneled CVCs |
| **Long-term intravenous medical treatment (>4 weeks)** | Single- or multi-lumen tunneled CVC; Port-á-cath |

[1] Abbreviations: CHC: central hemodialysis catheter; CVC: central venous catheter; PICC: peripherally inserted central catheter

# Different Catheter Materials

Throughout the years, CVCs have been made of different materials [42]. When first introduced into clinical practice in the 1940s, they were made out of polyethylene. However, the material did not only cause numerous infections, but it was also highly thrombogenic. This prompted further research and led to the utilization of other more biocompatible catheter material, such as polyurethane, polyvinylchloride, silicone elastomers, and polytetrafluoroethylene [42]. Currently, CVCs are made of either polyurethane or silicone, both presenting different properties and characteristics. Compared to silicone catheters, polyurethane catheters are stiffer but have thinner walls enabling larger lumens [43-45]. Furthermore, it is not uncommon for catheters to be coated or impregnated with different agents to reduce bacterial colonization and catheter-related bloodstream infections (CRBSI) [46].

The exploration of various catheter materials and coatings has resulted in more convincing evidence of their potential impact on the pathogenesis of both CRI and CRT [47-50]. However, only a few studies have assessed catheter blood compatibility. Hence, further research is needed to better understand the interrelation between catheter material and the pathogenesis of CRI and CRT.

## Catheter Insertion and Management

Throughout the years, numerous guidelines regarding placement and management of CVCs have been published [5, 51]. They serve to reduce CVC-related complications and optimize their management.

In general, it is recommended that catheterization is performed by an operator with confirmed skills for the insertion [52, 53]. The physical environment and location for catheter insertion should allow for aseptic techniques and the use of a standardized protocol, and an assistant is highly encouraged [51]. To prevent infectious complications, evidence-based hygiene insertion bundles are recommended [15, 16]. Aseptic preparation of practitioners, staff, and patients is recommended, and the selection of catheter insertion site should be based on clinical indication, site availability, and operator preferences. The most common sites for central venous catheterization are presented in **Figure 1** [54]. Optimized patient positioning, real-time ultrasound guidance, and the application of the Seldinger insertion technique using a guide wire [55], with a limited number of insertion attempts are recommended to prevent mechanical complications or injury associated with CVC insertion [5, 56-59]. Ultrasound can be used to choose an insertion site, help guide the needle towards its target vessel, verify the guidewire within the vessel and finally, confirm correct catheter tip positioning [60, 61]. Furthermore, it can serve to identify mechanical complications such as bleeding and pneumothorax [62]. The CVC should be fixated with sutures and the use of transparent occlusive dressing protecting the insertion site from infection is recommended [63-65].

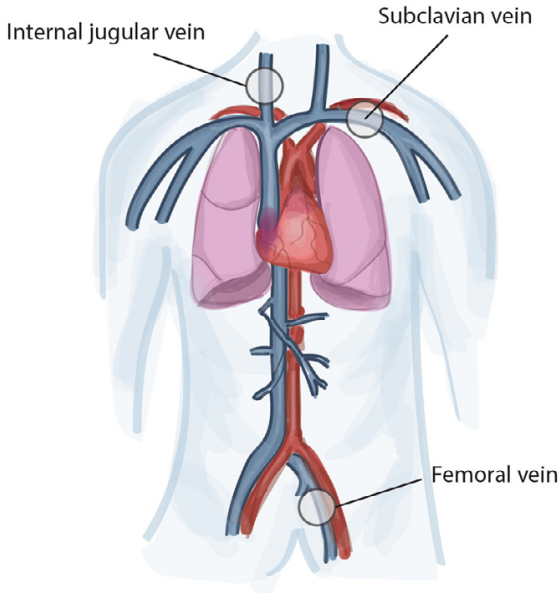


**Figure 1.** The most common sites for central venous catheterization. The contralateral veins can also be used for catheterization. Illustration by the author.

Catheter maintenance should be performed under aseptic conditions and include daily inspections of the insertion site with daily assessments of the clinical need for keeping the catheter [5, 51, 66]. Once used, the CVC lumen should be flushed with saline solution. It is recommended to aseptically change connectors, valves, lines, and CVC dressings periodically [19]. The catheters should be removed when an infection is suspected or promptly when no longer required [34, 67] .

In both international and Swedish guidelines, documentation of catheter insertion and maintenance is highly encouraged as it provides data for future control of CRI and quality assurance on CVC insertion and management [5, 51, 68, 69]. Documentation can be further facilitated by using pre-made CVC insertion and CVC management templates in the local electronic health record systems [70], which have become a well-established routine at all hospitals in Region Skåne in southern Sweden, involving a catchment area of two million inhabitants (https://sodrasjukvardsregionen.se) [68]. The local templates used are presented in **Figure 2** (in Swedish).

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Läkare Läkare

**Inläggande läkare**

**Indikation för CVK-kateter**

**Pågående antikoagulantiabeh.**

**Prokoagulantia före inläggning**

**Tid för inläggning**

**Plats för inläggning**

**Lokalisation**

**Inläggningsmetod**

**Kateterläge i huden**

**Anestesimetod**

**Lägeskontroll och användning**

**Produktfakta**

**Inläggningskomplikation**

**Blödning vid inläggning av CVK**

**Antal stick genom huden**

**Antal kärlpunktioner**

2023-03-16 14:06 **CVK-KATETER, SKÖTSEL (CVK-kateter) Intensivvårdsavdelning Lund (IvaSL)**
Läkare Läkare

**Komplikation första dygnet**

**DAGLIG BEDÖMNING**

**Behovsutvärdering utförd**

**Daglig inspektion utförd**

**Yttre kopplingsstycke bytt**

**PROBLEM OCH ÅTGÄRDER**

**Infektionstecken**

**Förband och hud**

**CVK-kateter, funktion**

**Användning utan blodretur**

**OMLÄGGNING**

**Omläggningsordination**

**Omläggning utförd**

**AVLÄGSNANDE AV CVK-KATETER**

**Datum för avlägsnande**

**Orsak till avlägsnande**

**Figure 2.** CVC insertion and management templates available in the electronic health record system (Melior) used at all hospitals in Region Skåne, Sweden (in Swedish).

# Catheter-Related Complications: Infections and Thrombosis

An inserted CVC will be recognized as foreign material by the host defense systems promoting inflammation and thrombus formation, which will create an environment that favors the development of CRI and CRT. These two conditions are complications associated with CVCs and studies have suggested their potential interrelation. A better insight into the various aspects of CRI and CRT could enable and lead the direction of further research within this field, and eventually, serve to reduce the occurrence of both.

## Catheter-Related Infections

### *Mechanism*

Once the CVC comes in contact with blood, a protein film—also known as a fibrin sheath - is formed on the material surface. Moreover, the inserted catheter directly creates a microbial entry point from the skin into the vessel, through which microorganisms can migrate along the catheter – either intra- or extraluminally – and form biofilm on the catheter surface [71, 72]. The ligand-like surface of the fibrin sheath further promotes biofilm development for bacteria [73, 74]. Sessile microbes on the CVC surface produce their own polymeric matrix, making them resistant to environmental factors such as antimicrobials [75]. A biofilm is difficult to eliminate and can cause and preserve a CRI as it enables detachment of microbial cell and/or biofilm fragments, which are then released into the bloodstream [76, 77].

As presented in **Figure 3** and according to prior studies, the following routes for catheter contamination are recognized [19, 34, 78]:

1. Migration of cutaneous organisms from the skin/at the insertion site (commensal skin flora) into the catheter tract and/or along the catheter surface with colonization of the catheter – either during or after insertion [19].

2. Direct contamination of the catheter lines and hubs, contaminated fluids/infusates or devices. The contamination usually comes from the caregivers handling the CVC [79].

3. Less commonly, the catheter might become seeded by microbes coming from another focus of infection (hematogenous spread) [76].

Migration of commensal skin flora along the catheter and direct contamination – sometimes from the hands of the care provider – are the most common causes of CRI [20]. Knowledge of the pathogenesis of these burdening infections has contributed to a better understanding of how to prevent CRIs and thus, develop guidelines that serve to prevent and minimize their occurrence.

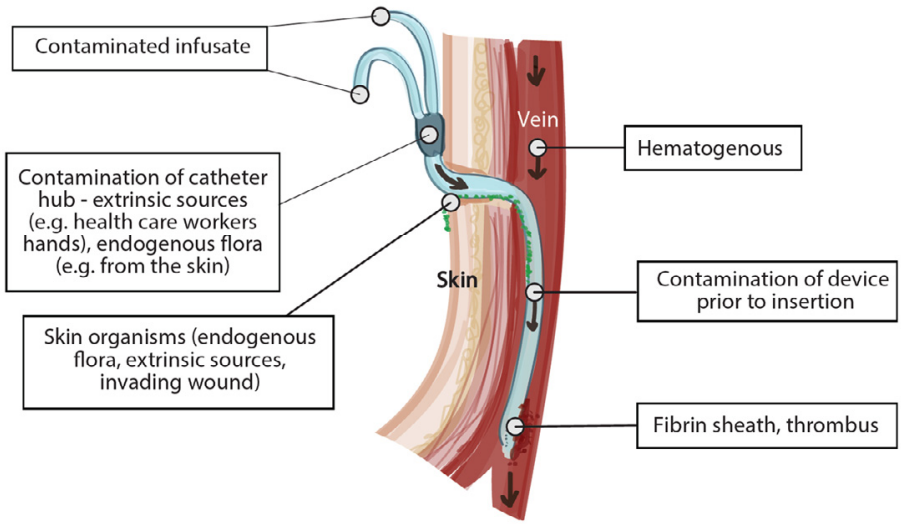


**Figure 3.** Potential routes of infection. Illustration by the author.

## *Definitions*

Definitions of CRIs are presented in **Table 2.**

**Table 2.** Summary of terminology and definitions of infections related to central venous catheters[1].

| Guidelines: | Terminology/definitions used |
|---|---|
| **Centers for Disease Control and Prevention (CDC)** [19, 80, 81] | **Local (exit-site) infection:** Signs of infection at insertion site or >2 cm from insertion site and along the tract of subcutaneous tunnel, +/- exudate, without BSI.<br>**CLABSI[2]:** Primary BSI in patient with CVC within 48h before developing BSI, with no other likely source of infection other than the catheter. |
| **Infectious Disease Society of America (IDSA)** [82] | **Colonization[3]:** Growth of >15 CFU or $>10^{22}$ CFU on tip cultures (semiquantitative vs. quantitative method, respectively).<br>**Local infection**: Signs of infection at insertion site, exudate yielding positive cultures, +/- BSI.<br>**CRBSI:** Local infection with growth of the same microorganism from >1 percutaneous blood culture and on catheter tip culture, with no other likely source of infection other than the catheter. |
| **European Centre for Disease Prevention and Control (ECDC)** [83] | **Colonization and local infection:** Signs of infection at insertion site, growth of >15 CFU on tip cultures) or $>10^3$ CFU (semiquantitative vs. quantitative method, respectively), exudate, without BSI.<br>**CRI:** Colonization with systemic signs of infection that improve within 48 hours after CVC removal.<br>**CRBSI:** BSI occurring 48 hours before or after CVC removal with growth of the same microorganism on blood and catheter tip cultures and/or culture from insertion site exudate. |
| **Swedish Association of Anaesthesia and Intensive Care (SFAI)** [5] | **Colonization:** Positive catheter tip culture.<br>**Local infection:** Signs of infection at insertion site, along the CVC tract, tunnel or port, +/- exudate, +/- BSI.<br>**CRI:** Positive tip culture with systemic signs of infection, with no other likely source of infection other than the catheter.<br>**CLABSI:** Primary BSI in patient with CVC within 48h before developing BSI, with no other likely source of infection other than the catheter.<br>**CRBSI:** Systemic infection with growth of the same microorganism from >1 percutaneous blood culture and on catheter tip culture, with no other likely source of infection other than the catheter. |
| **Other[4]** [67] | **sCRI:** Either a positive catheter tip culture or a positive percutaneous blood culture with >2/4 SIRS criteria at the removal of the CVC, with no other likely source of infection other than the catheter. |

[1] Abbreviations: BSI: bloodstream infection; CFU: colony-forming units; CLABSI: central line-associated bloodstream infection; CRBSI: catheter-related bloodstream infection; CRI: catheter-related infection; sCRI: suspected catheter-related infection; CVC: central venous catheter; SIRS: systemic inflammatory response syndrome.

[2] Centers for Disease Control and Prevention uses the term CLABSI for surveillance purposes and does not define CRBSI in their guidelines but has adopted and acknowledged the terminology used by IDSA for CRBSI.

[3] Also uses "significant growth of ≥1 microorganism in a quantitative or semiquantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub".

[4] The French Society of Intensive Care Medicine (SRLF)

One of the main difficulties in diagnosing CRI is the lack of a uniform definition, as illustrated by the diversity of definitions in **Table 2**. This was demonstrated in a large systematic review evaluating 191 studies reporting CRI, where Tomlinson et al. not only observed a variety of definitions, but also how many studies that fail to cite or report a definition at all [84]. The inconsistencies in defining the infectious outcomes related to CVCs have led to non-neglectable limitations in the interpretation of studies on infections related to CVCs:

First, the interchangeability between the wider terms CRI and bloodstream infection with the more specific term CRBSI can lead to studies overestimating the true incidence of CRBSI [19]. Second, a true CRBSI can be hard to establish as it depends on the availability of microbiologic methods. Moreover, it becomes even more problematic to diagnose a CRBSI in patients treated with antibiotics, as many bacteria are hidden from antibiotics in a biofilm and as the antibiotics may both kill the microorganisms released into the bloodstream and prevent their growth in blood cultures, even though a significant CVC-related infection with biofilm protected microorganisms is present. [26, 85].

Given the above, suspected CRI (sCRI), a broader definition, was used in Paper II. sCRI was recently proposed in expert consensus-based clinical practice guidelines [67]. A broader definition such as sCRI will lower the specificity but also increase the sensitivity for CRIs. This means that if sCRI is used, fewer true CRIs will be missed, at the expense of more cases classified as sCRI without true CRI.

The definitions used in this thesis are the following:

- **Colonization:** positive catheter tip culture regardless of clinical symptoms.

- **Local infection:** signs of inflammation (redness, swelling, heat, and/or pain) or pus at the insertion site with a positive culture taken from the insertion site.

- **sCRI:** either a positive catheter tip culture or a positive peripheral blood culture together with at least two of four criteria for Systemic Inflammatory Response Syndrome (SIRS) at the removal of the CVC, which cannot be explained by an infectious or non-infectious cause

other than the catheter *or* local inflammation at the insertion site as the only symptom.

- **CRI:** positive tip culture with at least two of four SIRS criteria upon catheter removal with no likely explanation for infection other than the catheter.

- **CRBSI:** bloodstream infection upon CVC removal with the same microorganism isolated on both the catheter tip and in the blood (within 48 hours prior to the removal of the CVC) in a patient fulfilling at least two of four SIRS criteria with no likely explanation other than the catheter.

- **SIRS criteria:**
  - Fever >38 or <36°C
  - Heart rate >90 beats per minute
  - Respiratory rate >20 breaths per minute
  - White blood cell count <4000/μL or >12 000/μL (this criterion was omitted in Paper II, as hematologic patients already have disturbed leukocyte counts due to reasons other than infections)

## *Epidemiology*

Infections related to central venous catheters are among the most frequent hospital-acquired infections, where European point prevalence studies have shown that 11% of hospital-acquired infections are bloodstream infections and 33% are related to indwelling CVCs [83, 86]. The reported incidence of CRI ranges between 0.6/1,000 and 20/1,000 catheter days, depending on definitions used, geographic region, and the studied patient population [26, 87, 88].

In European studies, the reported incidence of CRI and CRBSI in different populations ranges between 1.2-11.4/1,000 catheter days [14, 89]. In the United States, the incidence is estimated to be 1.2/1,000 catheter days [90]. In Scandinavia - where only a few investigations have addressed this issue - the estimated incidence of CRI is 0.6/1,000 catheter days, a relatively low incidence compared with the United States and other European and Asian countries, which exhibit higher incidence rates [26, 89, 91-93].

Since the introduction of numerous preventive measures, studies have shown that it is possible to almost eliminate CRI [15, 94-96]. Some studies have even

demonstrated that CRI can be completely eradicated [16]. Despite the continuous efforts to globally reduce the incidence of CRI, disparities between different regions of the world are still seen.

Infections related to central venous catheters are very burdening – not only for the patient – but also for the health care systems around the world. Many studies focusing on the estimated costs per CRI have been carried out around the world. In the United States, the cost of one CRI has been estimated to be between $11,971 and $75,000 [97-100]. The equivalent costs in Europe, there among Sweden, are estimated between €9,000 - €29,909 [101-103], whereas reports from Asia estimate costs between $3,528 and $57,090 [104, 105]. In developing countries, estimated costs are reported within lower ranges: between $4,888 and $11,591, with the main cost estimations being mainly attributable to the prolonged hospital stays [106, 107].

## *Diagnosing CRI: Clinical Signs and Cultures*

If an infection is suspected, cultures are required to diagnose and confirm the presence of CRI [19, 83].

Clinical signs associated with local infection at the catheter insertion site include pus from the insertion side with or without redness, tenderness or swelling. If exit site exudate is present, swab cultures are generally recommended [5].

If a CRI is suspected based on clinical signs of infection (according to SIRS) with no apparent source for bloodstream infection except the catheter, blood cultures are mandatory, even when the catheter does not need to be spared. It is generally recommended to draw blood from both the CVC and a peripheral vein, as differentiation between CRI and bacteremia is impossible when analyzing CVC-drawn blood exclusively [108]. Thus, guidelines recommend the following microbiological methods to diagnose CRI using blood cultures [5, 19]:

1. **Simultaneous and paired quantitative blood cultures:** "requires simultaneous blood cultures drawn both through the CVC and from a peripheral vein. A diagnosis of CRI is established if the culture drawn through the CVC versus the peripheral blood culture yields CFU counts of > 3-5:1" [109]. This method is considered to be the most accurate, with a sensitivity and specificity estimated to 87-93% and

97-100%, respectively [62, 108]. However, there are some limitations to this method – including that it is costly and labor intensive, especially in multi-lumen CVCs where blood samples from all lumina are recommended.

2. **Differential time to positivity:** the blood culture drawn from CVC becomes positive > 120 minutes before the simultaneously drawn peripheral blood culture. This method has a lower sensitivity and specificity (81-90% and 72-92%, respectively) and can be hard to interpret, but also influenced, if the patient is concomitantly treated with antibiotics, by the culture technique itself and the transportation time [82, 108].

To enable catheter tip culture, the catheter should be removed. Numerous guidelines recommend the following microbiological methods for catheter tip cultures to diagnose CRI and/or CRBSI [5, 19]:

1. **Semiquantitative CVC tip culture roll plate:** this method was first introduced by Maki et al. in 1977 and has been predominantly used ever since. It is the recommended method in Sweden [5]. In this method, the distal segment of the CVC is cut and rolled against a blood agar plate at least four times before being incubated overnight [110]. A tip culture yielding ≥15 CFU/mL is considered positive. The sensitivity and specificity of the method range between 45-90% and 90%, respectively [111]. However, the main limitation of this method is that it only cultures organisms from the external catheter surface and is thus not able to culture those embedded intraluminally [20].

2. **Quantitative method:** despite being the less frequently used method, it is the method used in all the studies of this thesis. It uses centrifugation, vortexing, or sonication to retrieve organisms from the internal and external catheter surface into a broth, which is diluted and streaked on blood agar plates for incubation [112]. A colony count of > $10^2$ (IDSA) - $10^3$ (European Centre for Disease Prevention and Control) is considered positive with a sensitivity and specificity of 82-93% and 89-97%, respectively [82, 83]. The main disadvantage of this method is that it might kill relevant sessile microbes.

These methods for catheter tip culture have proven useful for confirming CRI and CRBSI and are currently considered a gold standard. However, these cultures require at least 24 hours of incubation [82]. To circumvent this time-delay, a new technique—matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry - has emerged over the past decade and is now used as a tool for microbial species identification and diagnosis. This technique has the advantage of being very rapid – yielding results within an hour, as compared with 24 hours using the conventional methods – and has been shown to significantly decrease the time needed for pathogen identification. Furthermore, it is cheap and has significantly reduced laboratory costs [113].

The MALDI-TOF technique is frequently used to identify pathogens in blood samples – however – it is not as established on catheter tips. Nevertheless, standardization of the analysis method for catheter tips could make it useful to rule out CRBSI faster than using the gold standard culturing methods [114].

## *Causative Pathogens*

The most prevalent microbes responsible for CRI vary across countries and regions. In a European point prevalence survey of healthcare-associated infections, bloodstream infections were mostly caused by coagulase-negative staphylococci (16%), followed by *E. coli* (13%), *Staphylococcus aureus* (11%), *Klebsiella spp*. (11%), *Enterococcus spp.* (9.2%) and *Pseudomonas aeruginosa* (7.5%) [83]. In the United States, the most commonly isolated pathogens are the same, with the reported proportions varying slightly. In these reports, coagulase-negative staphylococci (34%), followed by enterococci (16%) and *Staphylococcus aureus* (10%) were most commonly isolated [115]. Pathogens such as *Pseudomonas spp.* and *Acinetobacter spp.* were more frequently isolated in European hospitals (7.5% and 4.0%, respectively), when compared with reports from the United States, where they were isolated in 3.1% and 2.2%, respectively. In contrast, *Candida spp.* were less frequently reported in Europe (7.0%) compared with the United States, where reports have demonstrated bloodstream infections to be caused by *Candida spp*. in 12% of cases.

In a Swedish prevalence report from 2014, the most commonly isolated pathogen reported to cause CRI were: coagulase-negative staphylococci (31%), *C. albicans* (24%), *S. aureus* (19%) and *E. faecalis* (9.0%). Species such as P. *aeruginosa* and *Acinetobacter spp.* represented less than 2.0% [26].

In developing countries, the reported numbers differ slightly. In point prevalence studies from Saudi Arabia, China and Brazil, pathogens such as *S. aureus* (14-39%), – including methicillin-resistant *Staphylococcus aureus* strains, *P. aeruginosa* (21-27%) and *Acinetobacter spp.* (11-27%) were more frequently reported [116-118].

The emergence of multiresistant bacteria has become a growing problem, not only in developing countries but also in Europe, where multiresistant bacteria constitute up to 30% of CRI-causing pathogens [119, 120]. In Sweden however, the prevalence of multiresistant bacteria is low [26].

In summary, the most prevalent microbes responsible for CRI overall are the following:

1. **Gram-positive organisms:** coagulase-negative staphylococci – being the most common one, followed by enterococci and *Staphylococcus aureu*s.
2. **Gram-negative bacilli:** *Klebsiella*, *Enterobacter*, *Pseudomonas*, *E. coli* and *Acinetobacter*.
3. ***Candida* species**

## *Risk Factors*

There are several known risk factors for CRI – divided into host factors and catheter factors where the latter includes insertion, material, and management [121]. A summary of reported risk factors is described in **Table 3**. In general, host factors are usually secondary to an underlying disease and/or immunosuppression, increasing the risk of infections.

Numerous studies have demonstrated that the site of catheter placement affects the risk of infection, with the subclavian site being associated with less risk as compared with the jugular and femoral sites [91, 122].

**Table 3.** Risk factors for catheter-related infections (CRI) in adults[1].

| **Risk factors** [5, 91, 121, 123-126] | |
|---|---|
| **Host Factors** | **Insertion and Catheter Factors** |
| **Age (increasing age)**<br>**Gender (varying results: female > male)**<br>**Underlying disease**<br>- AIDS<br>- low CD4 count<br>- immune deficiency with or without neutropenia<br>- gastrointestinal disease (short bowel syndrome)<br>- diabetes; hyperglycemic states<br>- malignancy<br>**Critical illness**<br>**Active infection at any other site**<br>**Systemic antibiotics**<br>**Admitted to a surgical ward**<br>**Extended hospitalization**<br>**Administration of blood products**<br>**Malnutrition**<br>- hypoproteinemia<br>**Hemodialysis**<br>**Trauma**<br>**Coexistence of other IV devices**<br>**Mechanical ventilation** | **Insertion**<br>- by house-staff or student<br>- difficult insertion; multiple cannulation attempts<br>- hygiene bundle compliance<br>- insertion in an old site over a guidewire<br>- site: femoral vein > jugular vein > subclavian vein<br>- cutaneous antiseptic used povidone-iodine > chlorhexidine<br>- topical anti-infective cream povidone iodine > mupirocin<br>- dressing used: non-impregnated > chlorhexidine gauze > transparent<br>- dressing disruption<br>- infected insertion sites<br><br>**Catheter**<br>- multi-lumen catheters<br>- catheter coating: non-coated catheters > coated catheters<br>- non-contamination resistant hubs<br><br>**Management**<br>- nurse staffing (low nurse per patient ratio)<br>- prolonged duration of catheterization<br>- frequent blood sampling<br>- total parenteral nutrition |

[1] Abbreviations: AIDS: acquired immunodeficiency syndrome; IV: intravascular

By studying and identifying risk factors associated with CRI, numerous preventive measures have been acknowledged.

## *Preventing CRI*

Previous studies have shown that strict basic hygiene routines while inserting and managing the CVC, together with the implementation of hygiene insertion bundles and other preventive measures, are infection-prevention strategies that successfully decrease CRI incidences over time [15, 19, 91]. These measures can be divided into education, training, staffing, preparations prior to catheter insertion, CVC insertion bundles, catheter site regimes, and catheter management. A summary of these preventive strategies is presented in **Table 4**.

It is generally recommended to individualize the choice of catheter and material – especially in high-risk patients, such as critically ill or immunosuppressed patients. Additional preventive measures such as the usage of chlorhexidine/silver sulfadiazine- or minocycline/rifampin-impregnated CVCs, have been shown to further reduce CRI in these cohorts [46, 127, 128]. Another alternative, which has shown promising results in pilot studies, is a novel catheter impregnation composed of noble metal alloy (Bactiguard, Stockholm, Sweden) [129]. However, further research is necessary to determine their effectiveness in preventing CRI.

**Table 4.** Strategies known to reduce catheter-related infections[1].

| **Measures to Prevent Catheter-Related Infections[2]** |
|---|
| **Education, training, and staffing** [52, 130, 131] |
| Education and training of healthcare personnel.<br>Periodical assessment and update of existing guidelines.<br>Assuring bundle compliance. |
| **Preparations prior to catheter insertion** [46, 54, 132] |
| Ensuring an aseptic location for CVC insertion.<br>Catheter selection based on indication for CVC (see **Table 1**).<br>Consider antimicrobial/antiseptic impregnated/coated CVCs (high-risk patients).<br>Choosing the most suitable access site[3]:<br>- CVC: subclavian > jugular > femoral<br>- CHC: jugular > subclavian > femoral<br>Consider prophylactic antibiotics prior to insertion (high-risk patients). |
| **CVC insertion bundles** [5, 15, 16, 19, 133, 134] |
| Patient and skin preparation: pre-operative shower, shaving insertion site, and pre-procedural wash of the insertion site (0.5% chlorhexidine or 70% alcohol).<br>Assure aseptic techniques with maximal sterile barrier precautions:<br>use of a cap, mask, sterile gown and gloves, sterile full body drape covering the patient.<br>Ultrasound-guided insertion (using a sterile sleeve).<br>Usage of procedural checklist.<br>Fixate the catheter with monofilament nylon suture.<br>Consider chlorhexidine dressing (high-risk patients). |
| **Catheter site regimens** [135, 136] |
| Use sterile, transparent semi-permeable dressing; replace when damp or loosened.<br>Replace the dressing every 3-7 days. |
| **Catheter management** [19, 137] |
| Daily inspections of the catheter site.<br>Skin cleansing (2% chlorhexidine) around the catheter site during dressing change.<br>Daily assessment of clinical need for CVC: remove promptly when no longer needed.<br>Flush CVC lumen with saline solution after usage.<br>Change catheter connectors, valves, and lines periodically.<br>If a CRI is suspected, remove or replace CVC and follow guidelines for diagnosing CRI. |

[1] Based on previously published data and on Swedish practical guidelines (Vårdhandboken).
[2] Abbreviations: CHC; central hemodialysis catheter, CVC; central venous catheter.
[3] Each insertion site (see **Figure 1**) has its disadvantages and disadvantages, with the femoral access site being most prone to CRI. However, the choice of insertion site will depend on the clinical indication, site availability and operator preference.

# Catheter-Related Thrombosis

## *Mechanism and Definitions:*

When a CVC is introduced to the circulatory system, endothelial disruption occurs, causing endothelial injury of the vessel wall with tissue factor release and subendothelial collagen exposure. Exposed collagen will present various surface receptors, including selectins, integrins, and glycoproteins, which promote platelet adherence to eventually form a platelet plug [138]. Moreover, the introduction of a foreign material into the body will immediately activate the innate immune system, attracting inflammatory cells to the catheter [139], inevitably forming a fibrin sheath covering the catheter surface. Both mechanisms will induce a local hypercoagulable state with blood flow stasis, which can enhance thrombus formation and subsequent endothelial impact – factors which are well described in Virchow's triad [24, 140-142]. Consequently, this can lead to a catheter-related thrombus [24, 142].

CRT can be classified into three types, as seen in **Figure 4** [143]:

- **Pericatheter fibrin sheath** – also known as a fibrin sleeve – a fibrin deposition with the growth of smooth muscle and endothelial cells on the catheter surface.

- **Intraluminal thrombus** – which can occlude the catheter lumen interrupting its function.

- **Mural thrombosis** – which could be secondary to the triggered hypercoagulable state, but also due to endothelial erosions from the catheter within the vessel. A mural thrombosis ultimately can lead to complete vein occlusion (causing a deep vein thrombosis) and irreversible damage to the vessel wall [143].

When the inserted CVC damages the intimal endothelium of the vein, a progressive inflammatory reaction may occur, promoting vessel wall thickening which may subsequently lead to vessel wall stenosis [9, 144].

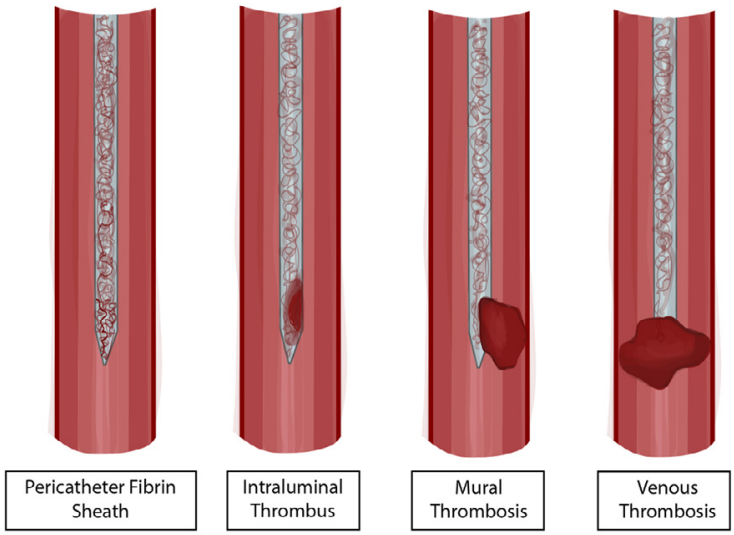


**Figure 4.** Types of CRT. There are three types, or stages, of CRT which could eventually lead to forming a venous thrombosis. Illustration by the author.

## *Epidemiology – CRT and Associated Complications*

Thrombotic complications associated with CVCs are some of the more commonly reported complications, reported with varying rates from around 5-18% [24, 29, 145-148], but they are generally believed to be underdiagnosed [23, 24, 145]. It has been demonstrated that CRT are estimated to account for 70-80% of all diagnosed upper extremity thrombosis and have shown to be responsible for 10% of all venous thromboembolisms [149]. Moreover, it can lead to the formation of pulmonary embolisms and deep venous thrombosis.

In a large retrospective study from 1991, where Diebold et al. reviewed 5,039 autopsy records, it was demonstrated that 30% of all subjects had pulmonary embolisms suspected to originate from the implanted catheters. In more recent studies, pulmonary embolisms of varying severity are estimated to occur in about 10-15% of all patients with a CVC [24, 146, 150].

Another thrombotic complication associated with CVC placement includes ischemic stroke, mainly observed in younger patients without diagnosed patent foramen ovale [151].

## *Risk Factors*

There are several known risk factors for CRT which can be divided into host factors and catheter factors. A summary can be seen in **Table 5**.

**Table 5:** Risk factors associated with catheter-related thrombosis.

| **Risk factors** [5, 24, 143, 149, 152][1] | |
|---|---|
| **Host Factors** | **Catheter Factors** |
| **Acquired hypercoagulability**<br>- HIT<br>- ovarian hyperstimulation<br>**Malignancy** (with/without chemotherapy)<br>**Existing comorbidities**<br>- diabetes<br>- obesity<br>**Use of certain** drugs (e.g., Thalidomide)<br>**Renal failure with/without dialysis**<br>**Inherited blood clotting disorders**<br>**Radiotherapy to the thorax**<br>**History of thrombosis**<br>**Sepsis** – including CRI<br>**Critical illness**<br>**Increased age** | **Catheter tip location/malpositioning**<br>- cranial to SVC > lower third of SVC<br>**Catheter diameter relative to the vein diameter**<br>**Type of catheter material**<br>**Multiple insertion attempts**<br>**Increased lumen diameter**<br>**Catheterization time** |

[1] Abbreviations: CRI: catheter-related infection**;** HIT: heparin-induced thrombocytopenia; SVC: superior vena cava

## *Diagnosis and Management*

As symptoms of CRT are usually absent, a thrombus is usually suspected following difficulty during aspiration of blood before use. It should be observed that other causes than CRT for catheter occlusion should first be considered, as they are managed differently. These include subcutaneous catheter kinking, catheter malpositioning, accumulation of certain infusates such as lipid emulsions, solutions with high or low pH, and calcium phosphate. On rare occasions, occlusion may be caused by pinch-off syndrome – a mechanical occlusion that happens when the central venous catheter is compressed between the clavicle and the first rib [153]. If no explainable cause is identified, occlusion by catheter thrombosis should be suspected [24].

Despite not being sensitive nor specific for CRT, a physical examination is always recommended. The clinical features associated with a CRT include [143, 149]:

- Swelling of head/neck or the ipsilateral limb
- Localized pain and/or numbness around the catheter area or the ipsilateral limb
- Jaw or shoulder pain
- Headaches
- Superficial venous distension
- Inflammation and/or signs of phlebitis surrounding the insertion site
- Erythema of the ipsilateral limb

Moreover, infection at the insertion site and/or CRI should always be considered and investigated accordingly, as it will influence the management once a concomitant thrombosis is present [150].

In the case of an intraluminal catheter occlusion due to thrombus formation, lumen patency may be restored by administering thrombolytic agents, such as Alteplase or Urokinase [5, 24, 154]. Studies have shown this measure to be effective in 90% of all catheters [34]. Nevertheless, further investigation is recommended if a thrombosis is clinically suspected or if lumen patency is not restored with simple measures [155].

The most common imaging modalities used to diagnose CRT include duplex ultrasound and/or contrast venography, which is considered the "gold standard" investigation [156, 157].

Once diagnosed, the need for the CVC should first be assessed. Moreover, the presence of underlying prothrombotic states such as inherited disorders of blood clotting and contraindications to anticoagulative treatment should be evaluated [34]. Consensus opinion recommends treating all diagnosed CRTs with systemic anticoagulation for a minimum of three months [158]. Randomized controlled trials regarding the optimal treatment of CRT are lacking. Low molecular weight heparin is the preferred agent for cancer patients. However, prospective randomized controlled trials are still needed to determine the most effective anticoagulant treatment in all other cohorts [24, 156].

## *Prevention*

Numerous studies on strategies to prevent CRT have been published [145, 158, 159]. It is generally recommended to select the smallest catheter for the purpose and ultrasound-guided insertions are encouraged to reduce the number of insertion attempts. To ensure correct catheter tip placement, post-procedural radiography is recommended [5, 69].

Over the years, clinical trials that aimed to assess the benefits of thromboprophylaxis to prevent CRT did not show any significant benefits in the reduction of CRT. Instead, the studies demonstrated an increased bleeding risk [160, 161]. Thus, anticoagulative treatment for routine prevention of CRT is not recommended. However, thromboprophylaxis may be appropriate for many reasons other than the CVC [156, 5].

Another debated topic is the potential thrombogenicity of various catheter materials. However, further studies are needed to determine any benefit of such catheters.

## *The Interrelation Between CRI and CRT*

Knowledge on the pathogenesis behind CVC-related complications has led to accumulated reports showing a potential interrelation between CRI and CRT [7, 10-12].

Given the prompt formation of a biofilm on the surface of the inserted CVC and the intimate relation between infection and coagulation, it is not surprising that thrombus formation is stimulated by the CVC [73]. Thus, bidirectional prevention of CRT and CRI could presumptively reduce the frequency of both conditions.

# Aims

The overall aims of this thesis were to improve the quality of CVC management, to increase patient safety and to explore the various aspects of CVC management that may cause CRI and CRT. The specific aims of the four studies presented in Papers I – IV were the following:

I. To investigate the incidence and the associated risk factors of CRI/CRBSI after the implementation of a simple hygiene insertion bundle in a non-selected cohort.

II. To examine the incidence and the associated risk factors of CRI/CRBSI in a selected, high-risk cohort: hematologic patients.

III. To evaluate the incidence and the associated risk factors of CRI/CRBSI in a non-selected cohort and to explore the feasibility of automatic data collection for future quality assurance.

IV. To demonstrate any pathological CVC-associated macro- or microscopic changes in the vein wall.

# Methods

This chapter presents the general and project-specific methods outlined in Papers I-IV. **Table 6** presents a general summary of the methods used.

# Study Design

**Table 6**. Overview of study design and methods[1].

| Paper | I | II | III | IV |
|---|---|---|---|---|
| **Design** | Retrospective cohort study | Retrospective cohort study | Retrospective cohort study | Prospective observational study |
| **Study Settings** | Skåne University Hospital (Lund) from January 2011 to December 2012. | Skåne University Hospital (Malmö and Lund) from March 2013 to February 2019 | All hospitals in Region Skåne from March 2019 to August 2020 | Skåne University Hospital from December 2021 to October 2022 (Lund) |
| **Informed Consent** | No (waived) | No (waived) | No (waived) | Not applicable |
| **Study Population** | Non-selected patients, over 8 years who receivied a CVC or CHC (n = 1,722) | Adult hematologic patients, over 18 years who received a CVC or CHC (n = 589) | Non-selected patients who received a CVC or CHC (n = 9,924) | Non-selected, deceased patients with a CVC or CHC (n = 12) |
| **Data Collection** | Manual | Manual | Automatic | Manual |
| **Main Outcomes** | Colonization, CRI and CRBSI | Mechanical complications, sCRI and CRBSI | Colonization, CRI and CRBSI | Macro- and microscopic changes observed at autopsy |

1 Abbreviations: CHC: central hemodialysis catheter; CRBSI: catheter-related bloodstream infection; CRI: catheter-related infection; CVC: central venous catheter; sCRI: suspected catheter-related infection.

# Data Collection

In Paper I and II, detailed data on catheter insertion and management from the template (**Figure 2**), together with all microbiological data, were manually extracted from each individual patient's chart in the electronic health record (Melior, Cerner, North Kansas City (MO), USA). The same method was applied for data collection in Paper IV, where we additionally extracted data from the autopsy reports. Extracted data was inserted into a compiled database.

In Paper III, data was extracted using an automated script-based search in the electronic health record (Melior, Cerner, North Kansas City (MO), USA) where CVC-insertions and management data were documented in insertion templates (**Figure 2**). Automatically extracted data was directly inserted into a compiled database (Excel, version 10, Microsoft, Santa Rosa, USA), where each individual insertion was merged with matching microbiological data and laboratory values obtained within 48 hours prior to the CVC removal. All insertions with data fulfilling the exclusion criteria were removed.

# Microbiological Procedures

In Paper I-III, microbiological procedures were applied according to our hospital's routines. According to the guidelines at our hospital, the catheter tip, together with a simultaneous peripheral blood culture should be sent for culture only when CRI is suspected. We analyzed CVC tip cultures and blood cultures retrospectively, during the defined study periods of each study.

The culture routine was the same in all three papers (I-III): CVCs were removed after site treatment with 0.5% chlorhexidine in 70% alcohol and the distal end of the CVC was submerged into a culture tube, where the distal 5 cm of the catheter (the tip) was cut off. The catheter tip was sonicated in 10 mL of broth and 0.1 mL of the broth was quantitatively cultured on blood agar plates. Growth of $>10^2$ CFU/catheter yielded a positive result.

The BACT/ALERT system (BioMérieux) was used for blood cultures. All bottles were incubated until microbial growth was detected or for a maximum of 5 days. In Paper III, the MALDI-TOF technique (described in the "Diagnosing CRI: Clinical Signs and Cultures" section) was used for bacterial specification.

# Project-Specific Methods

## Paper I

### *Patients and Inclusion:*

We retrospectively included all CVCs and central hemodialysis catheters inserted at the Department of Intensive and Perioperative Care at Skåne University Hospital, Lund, from January 2011 to December 2012. All catheters included were non-tunneled and inserted by an anesthesiologist at a centralized CVC clinic, the ICU, or in the operating room. We included all patients >8 years old, as this is the age limit for admission to our department. All peripherally inserted CVCs and ports were excluded, as their insertion requires a different technique with other hygiene precautions.

### *Implementation of a Hygiene Insertion Bundle:*

In January 2012, a standardized hygiene bundle for CVC insertions was introduced at our institution. Prior to this, the hygiene precautions applied at the time of catheter insertion were performed at the discretion of the inserting anesthesiologist. Although this procedure varied, it generally included one sterile wash of the insertion site with a solution of 0.5% chlorhexidine in 70% alcohol, sterile dressing, and sterile gloves. After the introduction of a hygiene insertion bundle in January 2012, additional hygiene precautions were added and included the placement of a clean bedsheet under the patient, a prewash of the insertion site with a chlorhexidine sponge, and then a sterile wash of the patient with 0.5% chlorhexidine in 70% alcohol, which was allowed to dry for two minutes prior to covering the patient with a large sterile drape. A maximal sterile barrier was worn by the inserting anesthesiologist (cap, mask, sterile gown, and sterile gloves), and a cap, mask, and apron were worn by the assistant. All catheters were fastened with sutures and dressed with a semipermeable dressing (Tegaderm HP; 3M Healthcare). An English version of the description of the new hygiene insertion bundle is presented in the appendix (Appendix S1) of Paper I.

### *Main Outcomes:*

The main outcomes were colonization, CRI, and CRBSI (see “Definitions” section for details).

## Paper II

### *Patients and Inclusion:*

In this study, we retrospectively included all adult hematologic patients (> 18 years old) who received a CVC or a central hemodialysis catheter at Skåne University Hospital (Malmö and Lund, Sweden), between March 2013 and February 2019. All catheters included were non-tunneled and inserted by an anesthesiologist at a centralized CVC clinic, the ICU, or in the operating room. All peripherally inserted CVCs and ports were excluded.

### *Catheter Insertion and Management:*

As these patients were considered to be at high risk for CVC-related complications, including CRI and bleeding, special precautions were taken during catheter insertion and CVC management. In addition to the standardized hygiene bundle implemented at our institution in 2012, these patients were evaluated for preprocedural coagulopathy (defined as platelet count <50 x $10^9$/L, prothrombin time (PT-INR) >1.8, or activated partial thromboplastin clotting time >43 s and equal to more than 1.3x upper normal value) and treated prophylactically if needed. Further details on CVC insertion and management are presented in Figure 1 of Paper II.

### *Main Outcomes:*

- Infectious complications: sCRI and CRBSI (see "Definitions" section for details).

- Moderate and severe mechanical complications, mainly including bleeding. Detailed definitions of the mechanical complications are described in Paper II (methods, outcomes).

## Paper III

### *Patients and Inclusion:*

In paper III, we retrospectively included all CVCs and central hemodialysis catheter insertions in non-selected patients, >8 years of age, from ten different hospitals within Region Skåne, Sweden, from March 2019 to August 2020. All

peripherally inserted CVCs and ports were excluded, as their insertion requires a different technique with other hygiene precautions.

### *Catheter Insertion and Management:*

CVCs were inserted and managed according to regional guidelines, which are well described in Paper I (Appendix S1).

### *Main Outcomes:*

The main outcomes were colonization, CRI, and CRBSI (see "Definitions" section for details).

## Paper IV

### *Patients and Inclusion:*

In this hypothesis-generating study we prospectively included 12 patients with a short-term CVC or central hemodialysis catheter, who were subject to autopsies at the Department of Pathology, Skåne University Hospital (Lund, Sweden) from December 2021 to October 2022.

### *Specimen Preparation and Microscopic Examination*

The autopsies and specimen collection were performed by one of the authors, assisted by an autopsy technician. The vein and the inserted CVC were carefully dissected from the point of catheter insertion to the right atrium. A longitudinal midline incision was performed, exposing the internal part of the vessel. All pathological or suspicious macroscopic findings, such as thrombi, were documented. The specimens, including loose pathological findings, were pinned to a Styrofoam plate and fixed in a 4% formaldehyde solution. The specimens were fixed for a minimum of 24 hours.

Transverse sections of 3-4 mm were subsequently cut at three predetermined vessel locations: the proximal portion (site of catheter insertion), the middle portion and the distal portion (leveled at the tip of the CVC). All sections were dehydrated and embedded in paraffin blocks, followed by sectioning at 3 μm and staining with hematoxylin and eosin stain and/or Elastica-Van Gieson stain. The slides were examined microscopically for histopathological changes. All findings were documented in the final autopsy report.

## *Main Outcomes:*

The main outcomes were macro- and microscopic changes observed at autopsy. The macroscopic outcome was thrombosis (yes/no).

The microscopic outcomes were:

1) Thrombus adherent to the vessel wall (yes/no)

2) Inflammation in the vessel wall, which was further classified into:

**0:** nothing visible
**1:** minimal or a few discernible inflammatory cells subjacent to thrombus
**2:** a modest number of inflammatory cells reaching deeper into vessel wall
**3:** marked cellular infiltration, with/without edema, reaching throughout the vessel wall

3) Fibrosis in the vessel wall, which was further classified into:

**0:** Nothing visible
**1:** minimal, hardly discernible presence of fibroblasts or early collagen formation
**2:** a mild collagenous thickening of the intima
**3:** an obvious increase in collagen and intimal thickening

# Statistical Analyses

All analyses were performed using SPSS versions 24 and 28 (SPSS Inc. IBM, New York, USA). The sample size was based on the number of available patients during the study periods for each separate study, and given their observational nature, power calculations were not performed. This is further discussed in the Discussion section under the subheading "Selection of Study Periods".

Statistical analyses were performed using data from the compiled datasets of each study. Results were expressed as median (range) or [interquartile range] for continuous variables and number (percentage) for categorical variables. As the sample size in Paper IV was small (n = 12) and due to its descriptive nature, no further statistical analyses were performed.

Papers I-III included further hypothesis testing. For univariate analyses of binary variables, the chi-square test or logistic regression was applied. Multivariable, logistic regression analyses were applied to analyze associations between dependent and independent variables. The selection of independent variables in these analyses was based on results from previous studies along with results from univariate analyses of each potential independent variable. The number of independent variables in the multivariable logistic regression models was limited to a maximum of one independent variable per ten events. The Hosmer-Lemeshow test was used to test the "Goodness of fit" for multivariable testing. A $P < 0.05$ was considered significant, and all statistical tests were two-tailed.

# Ethical Considerations

The studies included in this thesis were based on research involving human subjects and they were all approved by the Swedish Ethical Review Authority, Sweden, prior to study start. As the studies in this thesis included patient-sensitive data, we pseudo-anonymized all data by applying safeguards, such as de-identifying data sets with patient-specific keys which were separately stored, along with password-protected databases to protect patient confidentiality. All results were presented on a group level to eliminate the risk of identifying unique patients. Moreover, the researchers involved in all studies

were well aware that the processing of personal data entailed a compromise of privacy of the study participants.

The requirement for written informed consent for all studies was waived by the Ethical Review Authority. Instead, patients were given the option to opt out in local advertisements and posters with contact information for the responsible researchers.

In Paper IV, the requirement for informed consent was not applicable.

# Results

## Paper I

In this study, we included a total of 1,722 catheter insertions (94% CVCs and 6.0% central hemodialysis catheters) in 1,428 patients. Catheters were most commonly single-lumen (62%) and median days with catheter were 9 days (range 1-144). Baseline characteristics are presented in detail in Table 1 of Paper I.

Infection was suspected in 27% of all inserted catheters (457/1,722), prompting catheter removal and catheter tip culturing, and 4.9% of the tip cultures were positive (84/1,722). When the tip was sent for culture, simultaneous blood cultures were taken in 7.2% of all cases (124/1,722) and were positive in 2.1% (37/1,722). In 16 cases the same microorganism was identified on the catheter tip and the blood culture, and 15 of these cases met the criteria for CRBSI (0.9%, 15/1,722). The results of all cultures are presented in **Figure 5** below.

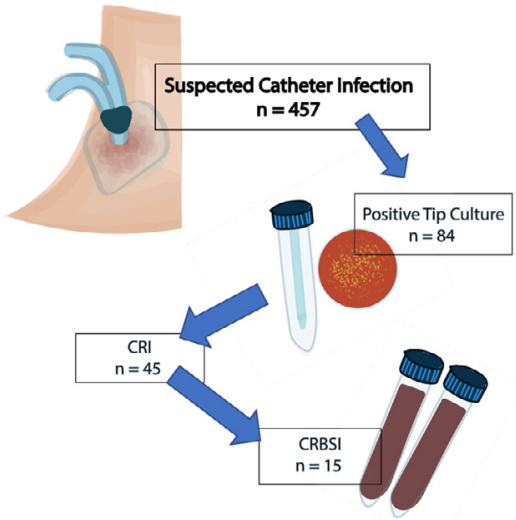


**Figure 5.** Culture results. In total, 457/1,722 catheters were suspected to be infected, with culture results yielding a prevalence of catheter colonization, CRI, and CRBSI of 4.9% (84/1,722), 2.6% (45/1,722) and 0.9% (15/1,722), respectively. Illustration by the author. Abbreviations: CRI: catheter-related infection; CRBSI: catheter-related bloodstream infection.

Once the hygiene insertion bundle was introduced, the rate of catheter tip colonization, CRI, and CRBSI decreased from 4.5/1,000 to 2.6/1,000, 2.7/1,000 to 1.1/1,000, and 0.8/1,000 to 0.5/1,000, respectively. Thus, the number needed to treat for catheter tip colonization, CRI and CRBSI was 40, 48 and 215, respectively. This means that 23 cases of catheter tip colonization, 19 cases of CRI, and four cases of CRBSI were avoided in our department the year after implementing the hygiene insertion bundle.

The overall incidence for CRI and CRBSI were calculated to be 1.86/1,000 and 0.62/1,000 catheter days, respectively.

The most common pathogens responsible for colonization, CRI and CRBSI are presented in Table 2 of Paper I. In summary, the most common pathogens isolated from catheter tip cultures (colonization) and responsible for CRI, were coagulase-negative staphylococci (61% and 49%, respectively). In CRBSI cases, *Staphylococcus aureus* (33% of CRBSI cases) and *Candida* species (27% of CRBSI cases) were the most common pathogens. Eleven percent of catheter tip cultures and 9.0% of CRI cases were polymicrobial. No multiresistant bacteria were isolated from either CVC or blood cultures.

To assess the associated risk factors of colonization, CRI and CRBSI, we performed multivariable logistic regression models. The implementation of a hygiene insertion bundle was the independent factor most strongly associated with significantly lower catheter tip colonization (P = 0.042) and CRI (P = 0.029) when compared to the year before implementation. An increase in the number of catheter lumens was also significantly associated with increasing catheter tip colonization and CRI. Catheters placed in the subclavian vein were associated with lower catheter tip colonization compared to those placed in the jugular vein (P = 0.036). Because there were few cases of CRBSI (n = 15) a multivariable analysis was not applicable.

Detailed results of the regression models are presented in Table 3 and Table 4 of Paper I.

# Paper II

In this retrospective study, we included a total of 589 catheter insertions (96% CVCs and 4.2% central hemodialysis catheters) in 387 hematologic patients. The median age was 57 years [interquartile range 41-68] and the median body mass index was 25 [interquartile range 23-29]. Preprocedural coagulopathy was present in 37% of all patients. The median days with catheter were 25 days [interquartile range 9-43]. The majority of catheters inserted were single-lumen (80%). Further details on baseline characteristics are presented in Table 2 of Paper II.

A summary of mechanical and infectious outcomes is presented below. Detailed data on mechanical and infectious outcomes per insertion site are presented in Table 3 of Paper II.

## Mechanical complications

In summary, mechanical complications were observed in 11% of all insertions (n = 64), with 8.5% classified as moderate (n = 50) and 2.4% classified as severe (n = 14), which of 11 were severe bleedings grade 3-4 and three pneumothoraces. Out of all moderate to severe bleedings, 13% occurred after an arterial puncture. Detailed data on pre-procedural coagulopathy and correction of hemostasis is described in Paper II, Figure 2 and Supplemental File 1.

## Infectious complications

In total, 69 patients were diagnosed with sCRI (12%), yielding an incidence of 3.7 sCRIs/1,000 catheter days during the study period. The incidence of sCRI in catheters placed in the subclavian vein was 3.3/1,000 catheter days and 5.6/1,000 catheter days in the internal jugular vein. There was no difference in the incidence of sCRI after subclavian compared to internal jugular insertions, (P = 0.58). Out of all 69 sCRIs, 12 were further classified as CRBSI, yielding a prevalence of 2.0% and an incidence of 0.64 CRBSI/1,000 catheter days.

In 54 out of all 69 (78%) cases with sCRI, the responsible pathogen was identified. In the other cases 15 cases, the classification of sCRI was based on positive cultures with the identified pathogen being described in the follow-up notes at the hematology department – hence, the actual microbiology results were missing. The most common pathogens isolated were coagulase-negative staphylococci (65%) and *Candida spp.* (2.9%). Other pathogens identified included: *S. aureus* (1.4%), *E. faecium* (1.4%), *E. faecalis* (1.4%), *P. aeruginosa* (1.4%), *S. grondonii* (1.4%) and *Rothia mucilaginosa.* A detailed description of each case with sCRI and CRBSI is shown in the Supplemental File 2 of Paper II.

## Associated risk factors for mechanical and infectious complications

The choice of variables for regression analyses is described in Paper II. For mechanical complications, pre-procedural coagulopathy (P <0.001), number of needle passes (P = 0.008), and arterial puncture (P = 0.004) were all independently associated with moderate to severe bleedings in the multivariable analysis. For infectious complications, high body mass index (P = 0.031) and male gender (P = 0.002) were both independently associated with sCRI in the multivariable analysis. Detailed results of the regression analyses are shown in Table 4 and Table 5 of Paper II.

# Paper III

During the 18 months studied, a total of 9,924 catheter insertions (96% CVCs and 4.0% central hemodialysis catheters) in 6,872 patients were included in the study. The majority of patients were male (61%) and the median age was 69 years [interquartile range 57-76]. The majority of catheters were triple-lumen (28%). Immediate complications after CVC insertion occurred in 5.5% of cases. For further details on baseline characteristics and outcomes, please see Table 1 in Paper III.

CRI was suspected in 23% of all CVCs (n = 2,304), prompting catheter tip cultures which yielded positive results in 11% of all cultured catheter tips (n = 257). The incidence of catheter colonization was 4.1/1,000 catheter days. Further, CRI was confirmed in 74 of all CVCs inserted (0.7%), yielding a CRI incidence of 1.2/1,000 catheter days. Simultaneous blood cultures and tip cultures were obtained in 667 inserted CVCs (6.7%), where these cultures yielded positive results in 69 cases (0.7%). However, only 20 cases met the criteria for CRBSI (0.2%), resulting in a CRBSI incidence of 0.3/1,000 catheter days.

The pathogens isolated in tip and blood cultures predominantly consisted of coagulase-negative staphylococci, where *S. epidermidis* was by far the most common species. In fact, *S. epidermidis* was the only responsible coagulase-negative staphylococcus for CRI and CRBSI. In tip cultures *S. epidermidis* was seen in 64% and *S. aureus* in 12% of all tip cultures. The microorganisms responsible for CRI and CRBSI respectively was *S. epidermidis* (66% and 40%), *S. aureus* (15% and 35%), various Gram-negatives (12% and 10%), and *Candida spp.* (12% and 10%).

To assess factors associated with infectious complications, regression analyses were performed, with detailed results presented in Table 4 of Paper III. In summary, male gender (P = 0.008 and P = 0.019, respectively) and increased number of catheter lumens (P <0.001) were independently associated with both catheter tip colonization and CRI. Increased number of days with a catheter (P <0.001) and CVCs inserted in patients admitted to a medical ward (P = 0.037) were associated with increased tip colonization, while catheters inserted in the subclavian vein were associated with decreased catheter tip colonization compared with insertions in the jugular vein (P <0.001). As the frequency of

CRBSI (n = 20) was low, no multivariable regression analyses were performed for CRBSI.

# Paper IV

In this study, we performed a total of 12 autopsies on seven female (58%) and five male (42%) patients with CVCs. The median age was 70 [interquartile range 63-76] and the median body mass index was 26 [interquartile range 22-28]. The most common comorbidity was cardiovascular disease (75%), followed by suspected or diagnosed malignancy (58%), hypertension (42%), and hyperlipidemia (42%). Apart from one patient (patient 3) who presented coagulopathy with prothrombin time, international normalized ratio ≥1.8, throughout the CVC period, all patients (92%) received routine thromboprophylactic Enoxaparin 40 mg daily. The main cause of death was cardiac arrest secondary to acute myocardial infarction (25%), pneumonia and/or acute respiratory distress syndrome (25%), or hypovolemic shock (17%).

All patients had polyurethane catheters inserted, and one patient had two CVCs in the same vessel: one polyurethane and one silicone catheter. Most CVCs had five lumens (54%) and were inserted in the internal jugular vein (92%), with the majority on the right side (77%). The median number of days with a catheter was seven [interquartile range 1.8-20]. All catheters were inserted using ultrasound guidance and no complications upon insertion were documented.

The macro- and microscopic changes observed are described in **Table 7**. Thrombi were observed macroscopically and microscopically attached to the CVC, as well as to the adjacent vessel wall (mural thrombus), in all cases (100%; see **Figure 6** and **Figure 7**). Microscopically, varying degrees of inflammatory changes in vessel walls were observed in all cases (see **Figure 7**), with varying degrees of fibrosis observed in eight cases (67%).

**Table 7.** Macro- and microscopic changes observed in the vessel wall on autopsy.

| | | Thrombus | | Vessel Wall Changes | |
|---|---|---|---|---|---|
| **Days with central venous catheter** | **Patient** | **Macroscopic (Y/N)** | **Microscopic adherent to the vessel wall (Y/N)** | **Inflammation (0–3)** | **Fibrosis (0–3)** |
| 1 | 1 | Y | Y | 3 | 0 |
| 1 | 6 | Y | Y | 2 | 3 |
| 1 | 7 | Y | Y | 1 | 1 |
| 2 | 12 | Y | Y | 1 | 2 |
| 3 | 2 | Y | Y | 2 | 2 |
| 7 | 8 | Y | Y | 1 | 0 |
| 7 | 9 | Y | Y | 1 | 0 |
| 12 | 3 | Y | Y | 3 | 2 |
| 19 | 5 | Y | Y | 3 | 2 |
| 22 | 4 | Y | Y | 3 | 3 |
| 22 | 10 | Y | Y | 1 | 0 |
| 25 | 11 | Y | Y | 3 | 3 |

**Degree of inflammation (microscopically)**
0 – nothing visible
1 – minimal or a few discernible inflammatory cells subjacent to thrombus
2 – modest number of inflammatory cells reaching deeper into vessel wall
3 – marked cellular infiltration, with or without edema, reaching throughout the vessel wall

**Degree of fibrosis (microscopically)**
0 – nothing visible
1 – minimal, hardly discernible presence of fibroblasts or early collagen formation
2 – a mild collagenous thickening of the intima
3 – an obvious collagen increase and intimal thickening

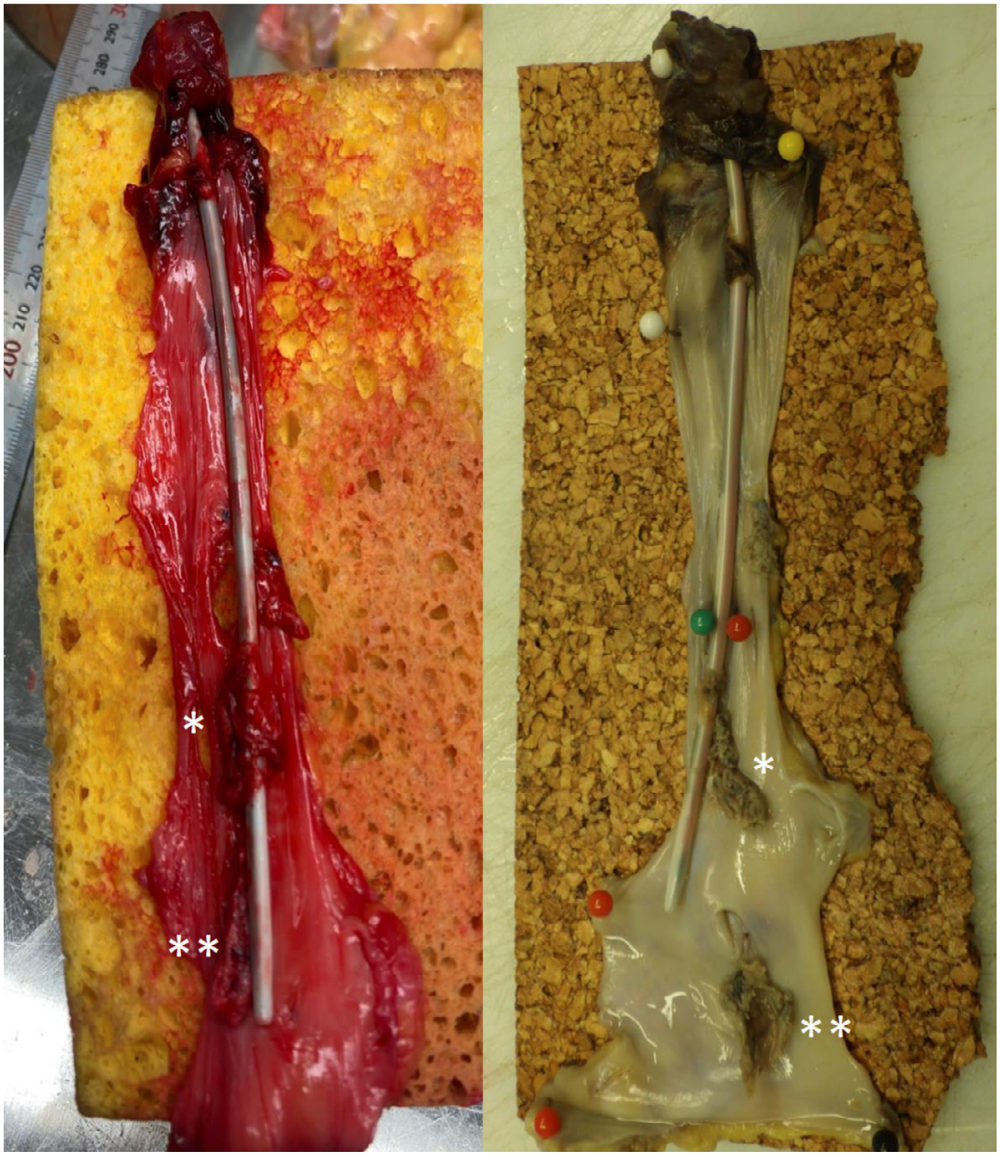


**Figure 6.** Macroscopic examination. Examples of typical thrombi attached to the central venous catheter (*) and to the adjacent vessel wall (**). Photographs were taken before and after formalin fixation. Photographs taken by the authors.

**Figure 7. Microscopic examination.**

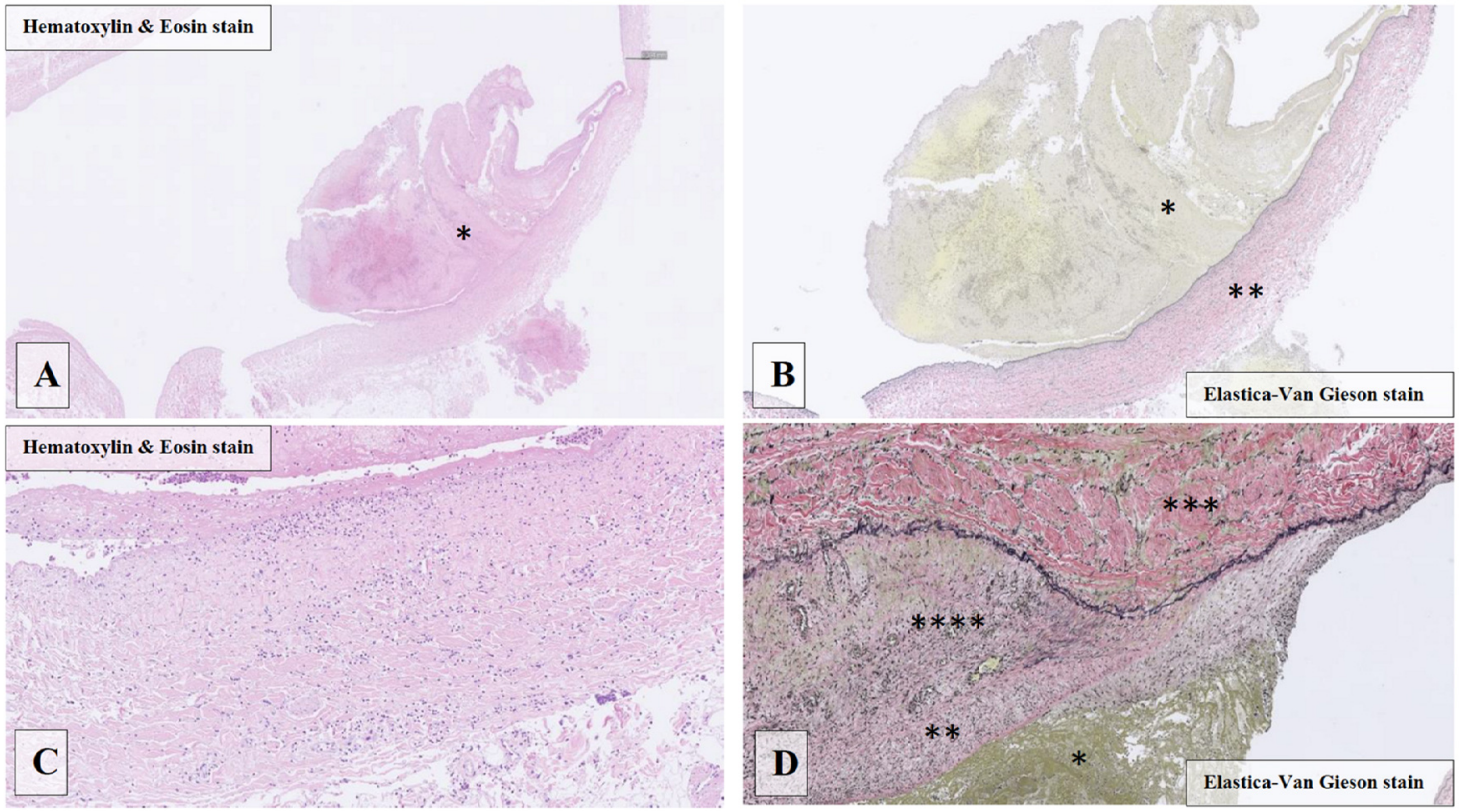


**Figure 7.** Microscopical changes observed at autopsy in the vein wall after central venous catheter insertion.Panels A and B show a large microscopical thrombus (*) adherent to the vessel wall. Marked inflammation (grade 3) with cellular infiltration and edema reaching throughout the vessel wall can be observed (**). Panel C represents a normal vessel wall, which can be compared with Panel D, demonstrating a severe degree of fibrosis with extreme thickening of the intima (***) and a marked increase in mucosal collagen (**) subjacent to the adherent thrombus (*) and a severe degree of inflammation with transmural infiltration of inflammatory cells (****). Pictures taken by co-author, Elisabet Englund.

# Discussion

By exploring the various aspects of CVC management that may cause CRI and CRT - including the local incidence and prevalence, the associated risk factors, and the histopathologic changes in the vessel wall after the indwelling of short-term CVCs - this thesis has contributed to new findings which could serve to improve the quality and patient safety of CVC insertion and management.

## Selection of Study Periods

The studied periods in each separate Paper were chosen and supported by a variety of factors.

The incitement for Papers I, II, and III was to quality review earlier CVC insertions during time periods when we had access to high-quality data. Hence, the sample size was not calculated based on prior studies or an expected outcome. Instead, the number of patients included in those studies was determined by the number of patients available during the study periods.

The study period in Paper I was limited to the access of historical standardized CVC insertion forms on paper. In Paper II the study period started at a time point when we received access to high-quality data. Paper III was based on automated data extraction and the study period started when we received automated access to the electronic documentation of CVC insertions.

Paper IV was a hypothesis-generating pilot study that may serve as the basis for sample size calculation in future studies.

# The Incidence and Prevalence of CRI

In Paper I, we observed a low incidence of CRI and CRBSI (2.7/1,000 catheter days and 0.8/1,000 catheter days, respectively) prior to the implementation of a simple hygiene bundle. The incidences were further reduced - from 2.7 to 1.1/1,000 for CRI and from 0.8 to 0.5/1,000 for CRBSI- after hygiene bundle introduction (P = 0.029), demonstrating its clinical importance.

However, the knowledge of bundle efficacy in reducing CRI was known prior to this study, where significant attention to simple hygiene bundles was given worldwide after the publication of Pronovost's classic study from 2006 [15]. This bundle consisted of hand washing, full barrier precautions during the CVC insertion, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and early removal of unnecessary catheters. The hygiene insertion bundle implemented in Paper I – which is presented in **Table 4** – was based on national and international guidelines [5, 15] and was similar to the ones present by Pronovost et al. However, they also included washing of the insertion site twice with 0.5% chlorhexidine in 70% alcohol, placing a clean sheet under the patient before insertion, and giving the assistant responsibility for compliance with the bundle´s use. In the study by Pronovost et al, there was no description of the insertion routines prior to the study intervention.

Given that Paper I was conducted a few years after the study by Pronovost et al, and that our department had already embraced the advantages of good insertion hygiene, it is reasonable to assume that even though existing hygiene insertion routines are acceptable, the additional simple hygiene precautions described in this study could have served as further prevention of CRIs.

Another potential factor for success in bundle introduction at our institution may have been the standardization of local CVC work processes – a measure that has shown a high success rate in reducing CRI [16]. Before its introduction, hygiene precautions were performed at the discretion of the inserting anesthesiologist. The new bundle led to a standardized workflow, which also resulted in the introduction of the CVC insertion and management template, presented in **Figure 2**. This has served as a quality assurance but also enables efficient data collection – which benefitted future research leading to Paper III.

In Paper III, a follow-up study conducted almost ten years after Paper I, we applied automated data scripts for effective data collection and demonstrated a sustained low incidence of CRI and CRBSI (1.2 and 0.3/1,000 catheter days, respectively). It should be noted that significant time elapsed between the two studies, where Paper III included significantly more cases (9,924 vs. 1,722) and an automated-data script extraction from the whole Region (vs. manual data extraction from only one hospital). However, a lower point estimate of CRI and CRBSI was still observed in Paper III when compared with Paper I - where the overall incidence was 1.86 and 0.62/1,000 catheter days.

Similar findings were observed in previous studies from 2006 and 2014, where Hammarskjöld et al. evaluated the incidence of CRI in Sweden. The first study (2006) demonstrated an incidence of CRI of 1.55/1,000 catheter days, whereas the second study (2014) confirmed a sustained low incidence of CRI and CRBSI after the six-year study period (2.2 and 0.6/1,000 catheter days, respectively) [26, 103]. The authors concluded that a CRI prevention program, led by an active CVC team, was the key factor in maintaining the low CRI rate over a long period of time. Another component that may contribute to a sustained low CRI incidence over time is continuous education on insertion bundles and CVC management [34]. In fact, previous studies have shown the importance of educational measures, including continuous staff training, measured and provided feedback on outcomes, and bundle compliance assessment, as they have led to an almost complete eradication of CRI [13, 16, 162].

In contrast to Papers I and III which included non-selected patients that received a CVC, Paper II was conducted to assess the CVC-related complications in selected, high-risk patients. Besides assessing mechanical complications, this study evaluated the incidence of sCRI after the insertion of non-tunneled, non-coated CVCs. The observed incidence of sCRI (3.7/1,000 catheter days) was in the range of infection rates previously reported, where the CRI and CRBSI incidences in similar cohorts as the present study ranged between 1.3 and 7.6/1,000 catheter days [124-126]. However, the incidence was higher than that of non-selected patients from the same hospital (as demonstrated in Papers I and III), underlining the importance of considering further precautions, such as daily inspections, evaluation of future needs, and choosing coated CVCs and dressings, to further avoid CRI in these susceptible hematologic patients.

Nevertheless, it should be noted that the definition of CRI is slightly different in Paper I and III compared to the definition in Paper II where sCRI was used. To enable better comparisons in the non-selected cohort studies (Paper I and III) the wider term CRI, together with the more specific term CRBSI, were chosen. In Paper II, however, the majority of patients were treated with intravenous antibiotics both prior to catheter insertion and throughout its usage, making the diagnosis of CRBSI problematic [26, 85]. As many organisms in significant CRIs are hidden from antibiotics in a biofilm on the catheter but killed by antibiotics if released into the bloodstream, blood cultures could yield false-negative results [85]. Therefore, the term sCRI suggested in recent expert consensus-based clinical practice guidelines [76], was chosen as a broader definition such as sCRI - used for patients concomitantly treated with broad-spectrum antibiotics - despite lowering the specificity, could increase the sensitivity for CRIs.

The pathogens isolated in cultures from Papers I-III were similar to those previously described – independent of the studied cohort – with coagulase-negative staphylococci representing most cases of CRI, both in Sweden and globally [26, 83, 103, 115, 116]. Nevertheless, there were some regional differences in pathogen growth when comparing the results from Paper I-III with previous studies on CRI [26, 103]. Hence, these findings could impact local infection management strategies to prevent certain pathogens from causing CRI. As an example, antifungal treatment could be considered when treating suspected CVC infections in regions with higher incidences of CRI caused by *Candida spp*.

Notably, there were no methicillin-resistant *S. aureus* or vancomycin-resistant Enterococci isolates in any of our studies. This reflects the low prevalence of these bacteria in the studied institutions and confirms the efficacy of the national antibiotic surveillance program (Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance; STRAMA), introduced in 1994, which has contributed a significant reduction in multi-resistant strains [163].

# Associated Risk Factors for CRI

Previously known risk factors for CRI, as presented in **Table 3**, were identified in Papers I-III.

In both Paper I and III, increased number of CVC lumens was independently associated with CRI, where each added CVC lumen increased the odds of CRI by approximately 63%. The increasing area of catheter material where microbes may adhere and the number of ports where microbes may be injected could explain this difference to some extent. These results are consistent with some prior studies [164, 165], although the results in the literature are conflicting [166]. It should be noted that no large study which adjusted for comorbidities and the degree of sickness has confirmed these findings. Also, the multivariable regression model used in both Papers did not adjust for these factors. However, studies on more homogenous groups of patients have indicated the benefits of choosing single-lumen over multi-lumen catheters in varied populations, including critically ill and cancer patients [164, 165]. In Paper II, the association of multi-lumen catheters and CRI was not observed in hematologic high-risk patients – however, this could be explained by the fact that the majority of patients received single-lumen catheters (80%). Thus, this finding advocates for minimizing the number of catheter lumens when choosing a CVC, where the need for extra lumens and type of catheter should be carefully evaluated according to the indication (**Table 1**) before insertion.

In Papers II and III, male gender was associated with sCRI and CRI, respectively. As shown in **Table 3**, the majority of reports link female gender with an increased risk for CRI. However, there are a few studies demonstrating the opposite [167]. In a prospective study by Moro et al., it was shown that men present an increased risk for skin colonisation at the CVC insertion site, which showed an increased risk of CRI, especially when using the jugular vein as the point of insertion [168]. Furthermore, beard growth and shaving may not only facilitate pathogen multiplication, but have also been observed to reduce adherence to wound dressing materials, suggesting an increased risk of bacterial contamination [169].

In Paper II, another host factor – obesity - was identified as a risk factor for sCRI in this high-risk cohort. Only a few studies have described obesity as a risk factor for CRI. In a recent meta-analysis including five relevant studies on both selected and non-selected cohorts, obesity was significantly associated with a higher risk for CRI [170]. Theories suggest that obese patients have an increased risk of CRI because of other obesity-related comorbidities and loss of physical markers and the long distance from the superficial structure to the central vessel making the CVC placement more difficult, which may cause physicians to hesitate replacing CVCs in obese patients [171]. Another possible explanation is the tendency towards increased perspiration in obese

patients, which can cause dressing disruption (as described in **Table 3**) [172, 173]. This underlines the importance of hygiene bundle compliance, especially when managing CVCs.

# Vessel Wall Changes Associated with Catheter Insertion

In Paper IV, we prospectively examined macro- and microscopic changes in vein walls with indwelling short-term CVCs, to demonstrate thrombus formation and varying degrees of inflammation changes in all cases, along with fibrosis in 67% of all investigated cases. Even if these results are not always clinically apparent, they are worrying, considering their potential consequences [11], especially in the context of a presumed interrelation between CRT and potentially life-threatening CRI [7, 9-12], but also because CRT has been described as causing other serious complications, including pulmonary embolisms [24, 146, 150].

The macro- and microscopic venous changes occurring after CVC insertion in human patients are previously described in a small study published by Forauer et al. in 2003 [174]. In a total of six specimens, thrombi with catheter-to-vein wall bridges were observed in all patients, with half of all patients presenting histological vessel wall changes equivalent to what we describe as grade 1–2 inflammation, whereas the other half presented changes corresponding to grade 3 inflammation with grade 0-3 fibrosis in the present study. Only minor inflammatory changes were seen in short-term catheters (inserted for fewer than 14 days). In contrast, we observed marked inflammatory and fibrotic changes in individuals with catheters in place for fewer than 14 days (as described in **Table 7**), indicating that severe vessel wall changes can occur independently of the length of catheterization. To the best of our knowledge, no other studies assessing these changes in humans have been conducted ever since.
In line with both Forauer's and our results, previous histological studies on animal models evaluating macro- and microscopic changes occurring with CVC insertion have demonstrated the formation of fibrin-containing thrombi attached to the fibrin sheaths covering the inserted CVC, known as sleeve-related thrombosis [147, 175]. Further examination of the fibrin sheath demonstrated a composition of smooth muscle cells and collagen covering a layer of endothelial cells, with presumed endothelial dysfunction and abnormal

anticoagulatory function [147]. Identical findings were described in the adjacent vein wall, where intimal hyperplasia was observed with subsequent vein wall thickening – noticed after about eight weeks – and inflammatory cell infiltration [147, 176-178] Moreover, the authors not only hypothesize that a CRT can spread to form mural thrombi through catheter-to-vein wall bridges, but also that the thrombi might lose support and detach from the sleeve, causing embolism [147, 179]. These findings highlight the potential harm of the CRTs demonstrated in the present study.

As thrombotic complications associated with CVCs are commonly reported [24, 29, 145-148] and given that all cases in the present study presented with macro- and microscopic thrombus with attachment to the vessel wall, there may be a large amount of subclinical CVC-related thrombosis, which reflects the speculations in some of the cited studies [11, 24, 148]. It should also be observed that, with the exception of one patient, all CRTs is in the present study developed in patients that were either given routine thromboprophylaxis or exhibited significant coagulopathy throughout the CVC time period.

Additionally, the inflammatory reaction caused by the CVC insertion itself can lead to inflammatory vessel wall changes, as demonstrated in 75% of our patients. These changes include inflammatory cell infiltration with increased oxidative stress, which may activate leukocytes releasing myeloperoxidase and activate the coagulation cascade [180]. This not only facilitates intramural thrombus formation but also induces smooth muscle cell hypertrophy, which may evolve into central vein stenosis, a finding most commonly reported in patients with large bore dialysis catheters [11, 144]. It should be noted that CRTs are known to cause CVC occlusion, leading to delays in treatment [24, 146].

Lastly, the blood compatibility of CVC materials may play an important role in the pathogenesis of both CRI and CRT. Although previous research has focused on preventing CRI, leading to the development of several antimicrobial-coated or impregnated CVCs [46, 181], a few modern studies have evaluated the thrombogenicity of different CVCs. In a study from 2018, a Chandler loop model with animal blood was used to compare the thrombogenic properties of various CVC materials. The results suggested that silicone catheters are more thrombogenic than polyurethane catheters [182]. Similar observations were made in a 2022 study, in which Thorarinsdottir et al. studied the hemocompatibility of six commonly used CVCs, also in a Chandler loop model using human blood. The study demonstrated a noticeable difference in thrombogenicity between various CVC materials [50]. Further

research, with a focus on developing CVC materials with less thrombogenic properties than the currently most used CVCs, is urgently needed.

# Limitations

## Adherence to Local Guidelines

Although guidelines for taking peripheral blood cultures when CRI was suspected did apply throughout Papers I-III, they were not always followed. This resulted in a drop-out of cases, particularly in Paper I, which could have led to a possible underestimation of the true CRBSI incidence.

The implemented hygiene insertion bundle, evaluated in Paper I, was widely distributed in the department, and the CVC insertion assistants noticed that the staff members were highly aware of the new hygiene insertion bundle. Moreover, individual adherence to all clinical guidelines during the studied periods in Papers I-III cannot be guaranteed. As an example, peripheral blood cultures were not taken in all cases with suspected CRI in Paper I, suggesting suboptimal compliance with culture recommendations.

## Data Collection

Despite being shown to be efficient, the sensitivity of the automated script-based data extraction from electronic health records was not investigated in Paper III.

## Missing Data

The retrospective nature of Papers I-III increases the risk of missing data. Although there is a well-established routine at the studied departments to document data related to CVC insertion and management using the premade templates (**Figure 2**), it cannot be ruled out that single insertions or certain CVC-related data was not documented and thus not included in the studies.

## Bias in Data Collection

In Papers I-III some comparisons of incidences between different time periods were made. This introduces a possible time-dependent bias as it cannot be ruled out that important factors, which may have affected the outcome, varied between the time periods.

## Defining Outcomes

The risks for incorrect classification of CRI concerns definitions. As SIRS criteria are not entirely specific for infection some patients may have been incorrectly evaluated with systemic infection and therefore incorrectly classified with CRI. Furthermore, the criteria included in the CRI definition of "no other likely cause of infection" is sometimes impossible to determine and may therefore have contributed to incorrect classifications.

## Statistical Methods

In Papers I-III, univariable and multivariable logistic regression analyses were used. Due to the low incidence of specific outcomes, particularly in Papers I and II, all potential risk factors involved in the development of colonization, sCRI, CRI, and CRBSI, could not be included in the multivariable regression analyses. Furthermore, we did not adjust for all patient comorbidities and although significant associations between factors and outcomes were observed, we cannot claim causality between the two due to the study design and lack of randomization.

Although we tried to correct for confounders in the multivariable logistic regression analyses and the Goodness of fit test was good, the presence of occult independent variables affecting the outcome in these Papers cannot be ruled out.

The sample size in Papers I-IV was based on the number of available insertions or autopsies during the study periods, meaning that the power of the results is uncertain.

# Conclusions

In summary, this work has demonstrated a low incidence of CRI and CRBSI in both non-selected and selected high-risk cohorts. The implementation of a simple evidence-based hygiene bundle in the non-selected cohort seemed to play an important role in reducing CRIs. In the thesis, it was also demonstrated that high-risk patients with hematologic malignancies had a higher risk for CRI after CVC insertion when compared with non-selected patients. Moreover, it served to confirm well-known and identify less well-known risk factors for CRI and CRBSI. The utilization of automatic data scripts enabled efficient data collection, suggesting this method could be useful for future analyses of CVC-related complications.

By studying the macro- and microscopic changes in the vessel wall after the indwelling of short-term CVCs, this thesis demonstrated that CRT was common and that adjacent inflammatory vessel wall thickening also occurred frequently. These findings are worrying, as CRT may cause life-threatening complications such as pulmonary embolisms.

# Future Perspectives

*Catheter-related infections: A Scandinavian observational study on the impact of a simple hygiene insertion bundle.*
Standardization of hygiene insertion protocols seems to be an effective measure to prevent CRI. There is a need for standardization of care bundles after CVC insertion, and for developing large-scale monitoring systems that can give feedback and guide further work in the battle against CRI/CRBSI.

*Central venous catheter-related complications in hematologic patients: An observational study.*
The incidence of CRI is higher in this cohort, as when compared with non-selected patients. As these patients seem to be at high-risk for developing CRI, further hygiene measures – such as using impregnated dressings and CVCs – could lead to a reduction in the infection incidence in this susceptible cohort. Moreover, a uniform definition for CRIs across studies would strengthen the quality of future reports and comparisons.

*Sustained low catheter related infection (CRI) incidence in an observational follow-up study of 9,924 catheters using automated data scripts as quality assurance for central venous catheter (CVC) management.*
Automated data scripts allow for efficient data collection. Thus, future follow-up studies on CRI incidence are highly encouraged for quality assurance purposes. Furthermore, a collaboration with computer scientists could help us develop unsupervised computational codes, serving to combine and convert automatically extracted CVC-related data with microbiological results and imaging technique results, to real-time reports on CRI incidence and CRT occurrence.

*Macro- and Microscopic Changes in Veins with Short-Term Central Venous Catheters: An Observational Autopsy Study.*
This hypothesis generating pilot study demonstrated that CRTs are surprisingly common. Although the sample size was small, the results may be used to design larger studies, including sample size calculation. Furthermore,

the clinical significance of the findings needs to be evaluated along with studies and the development of less thrombogenic CVC materials.

# Populärvetenskaplig Sammanfattning

Centrala venkatetrar är nödvändiga vid många situationer inom sjukvården, i synnerhet i intensivvårdssammanhang. De ger en direkt infart till den centrala cirkulationen och möjliggör att bedriva högkvalitativ vård. I Sverige läggs ungefär 50,000 centrala venkatetrar varje år, vilket gör det till ett av de vanligaste invasiva momenten vi utsätter patienter för inom slutenvården. Dessvärre är dessa katetrar även förknippade med en ökad risk för kateterrelaterade infektioner och kateterrelaterade tromboser, särskilt hos högriskpatienter. Varje dag med central venkateter ökar risken för infektion och trombos i kärlet där katetern ligger. Varje kateterrelaterad infektion förlänger både antalet dagar på intensivvårdsavdelningen samt det totala antalet sjukhusdygn, vilket inte bara ökar de totala sjukhuskostnaderna, utan även orsakar patienten ytterligare lidande. I studier har man dessutom visat att kateterrelaterade infektioner ökar risken att dö.

Under de senaste årtiondena har ett flertal studier undersökt förekomsten av kateterrelaterade infektioner och kateterrelaterade tromboser. Detta har bidragit till att man skapat internationella och nationella riktlinjer kring hantering av centrala venkatetrar, med huvudsyfte att minska antalet kateterrelaterade komplikationer. Dessa riktlinjer grundas på evidensbaserade rutiner, som i tidigare studier övertygande visat sig kunna reducera antalet kateterrelaterade infektioner och tromboser signifikant. Vidare, har man även visat att båda är möjliga att undvika. Trots att man i tidigare studier visat att kateterrelaterade infektioner är möjliga att undvika är tillståndet fortsatt bland det mest förekommande sjukvårdsrelaterade infektionerna.

Denna avhandling inkluderar fyra delarbeten med fokus att vidare utforska de olika aspekterna kring inläggning och handhavandet av centrala venkatetrar. De övergripande målen med avhandlingen har varit att belysa förekomsten av kateterrelaterade infektioner och tromboser, att undersöka riskfaktorer för att

tillstånden ska utvecklas samt att undersöka olika sätt att samla data för att extrahera antalet kateterrelaterade infektioner.

I det första delprojektet undersökte vi förekomsten av kateterrelaterade infektioner hos alla patienter som fått en central venkateter under två år på Skånes universitetssjukhus i Lund. Mitt i studietiden infördes en ny checklista med enkla hygienrutiner för att upprätthålla sterilitet vid inläggning av centrala venkatetrar. I denna studie var förekomsten av kateterrelaterade infektioner låg. Om den centrala venkatetetern var inlagd året efter införandet av hygien-checklistan var risken för kateterrelaterad infektion lägre. Analysen av data visade också att centrala venkatetrar med flera lumen (skänklar) innebar större risk för kateterrelaterad infektion.

I delprojekt II analyserade vi förekomsten av kateterrelaterade komplikationer bland hematologiska patienter, vilka anses ha en ökad risk för både blödning och infektioner. Resultaten visar att förekomsten av blödning och infektionskomplikationer var högre jämfört med andra patienter. Vidare, observerade vi att högt body mass index (BMI) samt manligt kön separat var relaterade till kateterrelaterade infektion.

I det tredje delprojektet, utvärderade vi förekomsten av kateterrelaterade infektioner bland 9,924 inlagda centrala venkatetrar hos alla patienter som fått central venkateter under ett och ett halvt år i Skåne. Data samlades in med hjälp av automatiserad extraktion från journalsystemen. Sammanfattningsvis var förekomsten av kateterrelaterade infektioner fortsatt låg. Vidare analyser visade att centrala venkatetrar med flera lumen samt manligt kön, separat ökar risken för kateterrelaterade infektioner.

I det fjärde delprojektet inkluderade vi tolv avlidna patienter med befintlig central venkateter, som var planerade för obduktion. Venen som den centrala venkatetern låg i undersöktes både med blotta ögat och med hjälp av mikroskop. Kateterrelaterade tromber observerades med båda metoderna hos alla patienter. Vidare, hittade vi varierande grad av inflammatoriska förändringar i samtliga fall och olika grader av fibros i en majoritet av patienterna.

Den övergripande slutsatsen är att man med hjälp av riktade insatser, såsom stärkta hygienrutiner och patientanpassat val av central venkateter, har en möjlighet att minska risken för kateterrelaterade infektioner. Vidare, verkar kateterrelaterade tromboser vara förvånansvärt vanligt förekommande. Med

hjälp av automatiserad datainsamling har datainsamlingsprocessen kunnat effektivisera. Detta sätt att extrahera data kommer att kunna vara mycket användbart både som verktyg i kvalitetssäkringsarbete och i framtida forskningsprojekt.

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# Paper I

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ORIGINAL ARTICLE

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# Catheter-related infections: A Scandinavian observational study on the impact of a simple hygiene insertion bundle

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**Background:** Catheter-related infections (CRIs) and catheter-related bloodstream infections (CRBSIs) are among the most frequent hospital acquired infections. CRI/CRBSI studies in Scandinavian cohorts are scarce. The primary aim of this study was to investigate the CRI/CRBSI incidence and the association between potential risk factors, including the introduction of a simple hygiene insertion bundle and CRIs at a large university hospital in Sweden.

**Methods:** We retrospectively included all patients aged 12 and above who received a central venous catheter (CVC) or a central dialysis catheter during a 2-year period, 1 year before and 1 year after the implementation of a simple hygiene insertion bundle. Microbiological data, including catheter tip cultures and blood cultures, were merged with CVC insertion data.

**Results:** A total of 1722 catheter insertions in 1428 patients were included. CRI and CRBSI incidence were 1.86/1000 and 0.62/1000 catheter days, respectively. In a multivariable regression model, the implementation of a simple hygiene insertion bundle was the independent factor most strongly associated with significantly lower CRI-incidence (95% confidence interval [CI] of odds ratio [OR] 0.23-0.92, $P$ = .029). Choosing multiple lumen catheters was associated with increasing CRI-incidence (95% CI of OR 1.11-2.39, $P$ = .013).

**Conclusion:** The incidence of catheter-related infections and catheter-related bloodstream infections in this Scandinavian cohort was low. The implementation of a simple hygiene insertion bundle seems to be an effective intervention for reducing catheter-related infections. The use of multiple-lumen catheters is associated with increased risk of catheter-related infections.

## 1 | INTRODUCTION

Central venous catheter-related infections (CRIs) and catheter-related bloodstream infections (CRBSIs) are among the most frequent hospital acquired infections, and they significantly increase mortality, length of stay, and hospital costs.[1,2] A previous Scandinavian study estimated the incidence of CRBSI at 0.6/1000 catheter days, a relatively low incidence compared with other European countries, which exhibit incidences between 1.2/1000 and 11.4/1000 catheter days in different patient populations.[1,3-5]

As soon as the central venous catheter (CVC) is inserted, a microbial entry point from the skin into the vessel is created. Thus, micro-organisms can migrate along the catheter by the extraluminal or intraluminal route causing soft tissue infection and subsequently leading to bloodstream infection.[6] The source of micro-organisms is often found in the patient's own commensal skin flora or by

contamination from care givers handling the CVC. Most infections are caused by coagulase-negative Staphylococci, *Staphylococcus aureus*, Enterococci, and *Candida* spp. Also, gram-negative strains such as *Escherichia coli*, *Klebsiella* spp, and *Pseudomonas aeruginosa* play an important role, because they have been identified as an increasing cause of CVC-related infections.[7,8]

It has been suggested that strict basic hygiene routines and the implementation of a hygiene insertion bundle are infection-prevention strategies that can successfully maintain a low incidence over a longer period of time.[5,9-12]

CRI/CRBSI studies in Scandinavian cohorts are scarce. Therefore, the primary aim of this study was to investigate CRI/CRBSI incidence and the association between potential risk factors, including the introduction of a hygiene insertion bundle and CRIs at a large university hospital in Sweden.

**Editorial Comment**

In this before-and-after Scandinavian cohort study, the incidence of central venous catheter infection diagnosis was low, and the implementation of a simple hygiene insertion bundle was associated with decreased incidence of catheter-tip colonization and catheter-related infections.

## 2 | METHODS

The study protocol was reviewed and approved by the Regional Ethical Review Board, Lund, Sweden (protocol 2012/773). The requirement for written informed consent was waived by the Regional Ethical Review Board. The manuscript was prepared according to the STROBE guidelines for observational studies.[13] This study was carried out at the Department of Intensive and Perioperative Care at Skåne University Hospital, Lund, Sweden.

### 2.1 | CVC-insertion

All patients who received a CVC or a central hemodialysis catheter (CHC) at our department from January 2011 to December 2012 were retrospectively included. The catheters included were inserted at our centralized CVC clinic, the intensive care unit, or the operating theatre. We included all patients over 8 years as that is the age limit at our department. All catheters were non-tunneled. No anti-microbial catheters were used. No prophylactic antibiotics were used. Indications for CVC insertion varied; they included parenteral nutrition, blood sampling, administration of drugs such as chemotherapy, or circulatory monitoring. Indications for CHC insertion were dialysis access or plasmapheresis. The preferred site of CVC insertion was the internal jugular vein. However, if the CVC was expected to remain in situ for more than 1 week and/or the patient was considered at increased risk of CRI/CRBSI by the inserting physician (eg, patients receiving chemotherapy), the subclavian vein was preferred. Catheters were inserted by anesthesiologists with varying degrees of experience (residents and specialists). Peripherally inserted central venous catheters and ports were excluded as they included a different inserting technique and different hygiene precautions.

### 2.2 | Implementation of hygiene insertion bundle

Hygiene insertion bundles have been shown to prevent or reduce CRIs and CRBSIs.[12,14-16] In January 2012, a standardized hygiene bundle for catheter insertion was introduced at our institution. Before January 2012, hygiene precautions utilized at the time of CVC insertion were performed at the discretion of the inserting anesthesiologist. Although this procedure varied, it generally included one sterile wash of the insertion site with a solution of 0.5% chlorhexidine in 70% alcohol, sterile dressing, and sterile gloves. After the introduction of a hygiene insertion bundle in January 2012, the CVC-insertion assistant was responsible for compliance with the application of the bundle. Moreover, the new hygiene insertion bundle included the placement of a clean bedsheet under the patient, a prewash of the insertion site with a chlorhexidine sponge, and then a sterile wash of the patient with 0.5% chlorhexidine in 70% alcohol, which was allowed to dry for two minutes prior to covering the patient with a large sterile drape. A maximal sterile barrier was worn by the inserting anesthesiologist (cap, mask, sterile gown, and sterile gloves), and a cap, mask, and apron were worn by the assistant. All catheters were fastened with sutures and dressed with a semipermeable dressing (Tegaderm HP; 3M Healthcare). A description of the new hygiene insertion bundle is presented in an English version in the appendix (Appendix S1).

### 2.3 | Data collection and culture routines

At our department the cannulation procedure is documented on a standardized insertion form, which includes information regarding the patient's age and gender, the site and date of insertion, the number of catheter lumens, the place and indication of CVC insertion, and primary diagnosis at insertion. All CVCs/CHCs registered in our registry in 2011 and 2012 were included. Microbiological data were thereafter extracted from the accredited microbiology laboratory at the hospital using an automated script. Microbiological data were then merged with insertion data from the standardized insertion form into a database. According to guidelines in our hospital, the catheter tip, together with a simultaneous peripheral blood culture should be sent for culture only when CRI is suspected.

### 2.4 | Definitions

Definitions were according to clinical guidelines by the Swedish Society of Anesthesiology and Intensive Care Medicine.[14] CVC colonization was defined as a positive tip culture regardless of clinical symptoms. CRI was present if the catheter-tip culture was positive and the patient had at least two of four systemic inflammatory

response syndrome (SIRS) criteria (fever >38 or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or white blood cell count >12 000/μL or <4000/μL) upon CVC removal with no likely explanation other than the catheter. CRBSI was defined as a bloodstream infection upon CVC removal with the same micro-organism isolated on both the catheter tip and in the blood (within 48 hours prior to the removal of the CVC) in a patient fulfilling at least two of four SIRS criteria with no likely explanation other than the catheter.

### 2.5 | Cultures

CVCs were removed after site treatment with 0.5% chlorhexidine in 70% alcohol. The distal end of the CVC was submerged into a culture tub, and the distal 5 cm was cut off. CVC tips were sonicated in 10-mL broth, and 0.1 mL of the broth was quantitatively cultured on blood agar plates.[17] Growth of $>10^2$ CFU/catheter was considered significant colonization. The BACT/ALERT system (BioMérieux) was used for blood cultures. All bottles were incubated until microbial growth was detected or for a maximum of 5 days.

### 2.6 | Statistical analyses

Results were expressed as median (range) for continuous variables and number (percentage) for categorical variables. Multivariable logistic regression analysis was applied to identify independent factors associated with catheter colonization and CRI. The Hosmer-Lemeshow test was used to test goodness of fit for multivariable testing. A $P < .05$ was considered significant, and all statistical tests were two-tailed. We performed all analyses using SPSS 24 (SPSS Inc.).

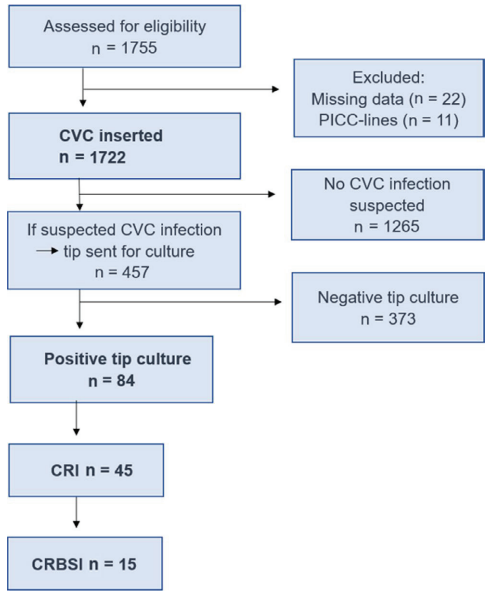


**FIGURE 1** Flowchart showing the selection of CRI and CRBSI cases. Abbreviations: CRBSI, catheter-related blood stream infection; CRI, catheter-related infection. CRI was defined as having at least two of four systematic inflammatory response syndeome (SIRS) criteria present, with no likely explanation other than the catheter. CRBSI was defined as having the same micro-organism isolated on both the catheter tip and in the peripheral blood culture and at least two of four SIRS criteria, with no likely explanation other than the catheter

## 3 | RESULTS

The patient selection is shown in Figure 1. A total of 1722 catheter insertions (94% CVCs and 6% CHCs) in 1428 patients (52% male, median age of 66 years) were registered (Table 1). Catheters were most commonly single lumen (62%), and the most-preferred insertion site was the jugular vein (76%). The median catheter duration time was 9 days (range 1-144). The baseline characteristics of catheters inserted before the implementation of a hygiene insertion bundle were similar to the characteristics of those inserted after the implementation (Table 1).

One fourth of the catheter tips (n = 457) were sent for culture at removal, and 18% of the tip-cultures (n = 84) were positive (Figure 1). Sixty-nine percent of the patients were on antibiotics when the CVC tip was sent for culture. CRI was present in 45 (2.6% of the 1722 catheters) of the cases, with an incidence of 1.86/1000 catheter days. When the tip was sent for culture, a simultaneous blood culture was taken in 124 cases and was positive in 37 cases. In 16 cases the same microbe was identified on the catheter tip and in the blood culture, and 15 of these cases (0.9% of the 1722 catheters) met the CRBSI criteria, yielding an incidence of 0.62/1000 catheter days. In 18 cases the blood culture was positive when CVC tip culture was negative. The rate of catheter-tip colonization, CRI, and CRBSI decreased from 4.5/1000 to 2.6/1000, 2.7/1000 to 1.1/1000, and 0.8/1000 to 0.5/1000, respectively, after implementation of the hygiene insertion bundle. Number needed to treat for catheter-tip colonization, CRI, and CRBSI was 40, 48, and 215, respectively. This means that 23 cases of catheter-tip colonization, 19 cases of CRI, and 4 cases of CRBSI were avoided in our department the year after implementing the hygiene insertion bundle.

Microbial isolation from central venous catheter-tips and patients with CRI and CRBSI are shown in Table 2. Overall, the micro-organism most frequently isolated from the catheter-tip was coagulase-negative staphylococci (61% of positive catheter-tip cultures) and *Staphylococcus aureus* (11% of positive catheter-tip cultures). Gram-negative bacteria were present in 15% of positive catheter tip cultures. The most frequently isolated gram-negative pathogens (presented as a percentage of positive catheter-tip cultures) were

**TABLE 1** Characteristics of patients and central venous catheters before and after implementation of the hygiene insertion bundle

| | Before bundle | After bundle | All |
|---|---|---|---|
| Central venous catheters, total | 804 (47%) | 918 (53%) | 1722 |
| Patients, total | 675 (47%) | 753 (53%) | 1428 |
| Age | 65 (13-95) | 66 (12-99) | 66 (12-99) |
| Gender, male | 437 (54%) | 456 (50%) | 893 (52%) |
| Days with catheter | 9 (1-106) | 8 (1-144) | 9 (1-144) |
| Type of catheter | | | |
| CVC | 739 (95%) | 826 (93%) | 1565 (94%) |
| CHC | 39 (5%) | 62 (7%) | 101 (6%) |
| Number of lumens | | | |
| One | 519 (67%) | 507 (57%) | 1026 (62%) |
| Two | 149 (19%) | 265 (30%) | 414 (25%) |
| Three | 85 (11%) | 93 (11%) | 178 (11%) |
| Four | 19 (3%) | 19 (2%) | 38 (2%) |
| Site of insertion | | | |
| Jugular vein | 586 (77%) | 650 (75%) | 1236 (76%) |
| Subclavian vein | 165 (22%) | 206 (23%) | 371 (23%) |
| Femoral vein | 10 (1%) | 14 (2%) | 24 (2%) |
| Place of CVC insertion | | | |
| ICU | 132 (17%) | 139 (16%) | 271 (17%) |
| CVC clinic | 368 (47%) | 395 (45%) | 763 (46%) |
| Operating theater | 272 (35%) | 329 (38%) | 601 (36%) |
| Patients ward | 3 (1%) | 9 (1%) | 12 (1%) |
| Patient´s department at insertion | | | |
| Medical ward | 292 (36%) | 328 (36%) | 620 (36%) |
| Surgical ward | 365 (46%) | 438 (48%) | 803 (47%) |
| ICU | 146 (18%) | 151 (16%) | 297 (17%) |
| Indication for CVC insertion | | | |
| Chemotherapy | 147 (19%) | 180 (20%) | 327 (20%) |
| Major operation | 202 (26%) | 275 (31%) | 477 (29%) |
| Fluid, nutrition, antibiotics | 311 (40%) | 266 (30%) | 577 (34%) |
| ICU care | 77 (10%) | 103 (12%) | 180 (11%) |
| Dialysis | 34 (4%) | 55 (6%) | 89 (5%) |
| Plasmaferesis | 8 (1%) | 12 (1%) | 20 (1%) |

*Note:* Data are presented as median (range) or number (percentage). "Bundle" refers to the hygiene insertion bundles introduced in January 2012. Missing data: number of lumens (n = 66), site of insertion (n = 91), place of insertion (n = 75), patient's department at CVC insertion (n = 2), indication for CVC insertion (n = 52).
Abbreviations: CVC, central venous catheter; CHC, central hemodialysis catheter; ICU, intensive care unit.

*Pseudomonas aeruginosa* (6%), *Klebsiella* species (3%), and *Serratia marcenes* (3%). *Candida* species were present in 8% of positive-tip cultures. A similar pattern was seen in patients with CRI, although the frequency of *Staphylococcus aureus* (19% of positive catheter-tip cultures) and *Candida* species (12%) was higher. In CRBSI cases, *Staphylococcus aureus* (33.2% of CRBSI cases) and *Candida* species (26.6% of CRBSI-cases) were the most common pathogens. Coagulase-negative staphylococci and gram-negative bacteria were present in 20% of the CRBSI cases. Eleven percent of catheter-tip cultures and 9% of CRI cases were polymicrobial. No multiresistant bacteria were isolated from either CVC or blood cultures.

We analyzed the determinants of catheter-tip colonization and catheter-related infection using a multivariable logistic regression model (Tables 3 and 4). The implementation of a simple hygiene

insertion bundle was the independent factor most strongly associated with significantly lower catheter-tip colonization (95% CI of OR 0.34-0.98, $P$ = .042) and CRI (95% CI of OR 0.23-0.92, $P$ = .029) when compared with the year before implementation. An increase in the number of catheter lumens was also significantly associated with increasing catheter-tip colonization and CRI. Catheters placed in the subclavian vein were associated with lower catheter-tip colonization compared to those placed in the jugular vein (95% CI of OR 0.24-0.95, $P$ = .036). Because there were few cases of CRBSI (n = 15) a multivariable regression model was not applicable. A description of patients with CRBSI is presented in Table 4.

**TABLE 2** Microbial isolation from central venous catheter-tips and patients with CRI and CRBSI

| Organism | Catheter-tip n = 93 | CRI n = 49 | CRBSI n = 15 |
|---|---|---|---|
| Gram-positive bacteria | | | |
| *Staphylococcus* species (CoNS) | 56 (61) | 24 (49) | 3 (20.1) |
| *Staphylococcus aureus* | 10 (11) | 9 (19) | 5 (33.2) |
| *Enterococcus faecalis* | 3 (3) | 2 (4) | 0 (0.0) |
| *Enterococcus faecium* | 1 (1) | 1 (2) | 0 (0.0) |
| *Corynebacterium striatum* | 1 (1) | 1 (2) | 0 (0.0) |
| Gram-negative bacteria | | | |
| *Klebsiella* species | 3 (3) | 1 (2) | 0 (0.0) |
| *Serratia marcenes* | 3 (3) | 1 (2) | 1 (6.7) |
| *Escherichia coli* | 1 (1) | 1 (2) | 0 (0.0) |
| *Pseudomonas aeruginosa* | 6 (6) | 1 (2) | 1 (6.7) |
| *Enterobacter cloacae* | 2 (2) | 2 (4) | 1 (6.7) |
| Yeast | | | |
| *Candida* species | 7 (8) | 6 (12) | 4 (26.6) |

*Note:* Data are presented as number (percentage). About 11% of catheter tip cultures and 9% of CRI cases were polymicrobial.
Abbreviations: CRI, catheter-related infection; CRBSI, catheter-related blood stream infection; CoNS, coagulase-negative staphylococci.

## 4 | DISCUSSION

In this Scandinavian observational study, we demonstrated that the incidence of CRI (1.86/1000 catheter days) and CRBSI (0.62/1000 catheter days) were low. Furthermore, we demonstrated that the introduction of a simple hygiene insertion bundle was associated with decreased incidence of catheter-tip colonization and CRI and that large-bore catheters with multiple lumens were associated with increased incidence of catheter-tip colonization and CRI.

The rate of CRI decreased from 2.7/1000 to 1.1/1000 catheter days after the implementation of a simple hygiene insertion bundle in this study. The introduced hygiene insertion bundle was based on recommendations from the Swedish Society of Anesthesiology and Intensive Care Medicine, was implemented with low cost and involved no new staff or expensive equipment.[14] Before implementation of the hygiene insertion bundle, hygiene precautions taken at the CVC insertion were performed at the discretion of the inserting anesthesiologist. The new bundle introduced included standardization of the insertion routines. A key factor of the bundle's success may have been that the CVC-insertion assistant, after the introduction of the new hygiene insertion bundle, was educated about the bundle and made responsible for compliance with its use.

The bundle used in the classic study by Pronovost et al[12] consisted of hand washing, full-barrier precautions during the insertion, cleaning the skin with chlorhexidine, avoiding the femoral site if

**TABLE 3** Catheter-tip colonization.

| Independent variable | No n = 373 | Yes n = 84 | Multivariable analysis OR | 95% CI | *P*-value |
|---|---|---|---|---|---|
| Age | 60 (16-93) | 62 (18-92) | 1.01 | 0.99-1.03 | .092 |
| Male gender | 188 (50) | 51 (61) | 1.50 | 0.88-2.54 | .136 |
| Days with catheter | 14 (1-144) | 13 (1-140) | 1.01 | 0.99-1.02 | .607 |
| Site of insertion | | | | | |
| Jugular vein | 213 (59) | 63 (79) | — | — | — |
| Subclavian vein | 140 (39) | 16 (20) | 0.47 | 0.24-0.95 | .036 |
| Femoral vein | 9 (3) | 1 (1) | 0.28 | 0.03-2.27 | .232 |
| Number of catheter lumens | — | — | 1.61 | 1.18-2.19 | .002 |
| CHC vs CVC | 40 (11) | 16 (20) | 1.93 | 0.94-3.96 | .073 |
| After bundle | 191 (51) | 34 (41) | 0.58 | 0.34-0.98 | .042 |

*Note:* Data are presented as median (range) or number (percentage). "Bundle" refers to the hygiene bundle introduced in January 2012.
Abbreviations: OR, odds ratio; CHC, central hemodialysis catheter; CI, confidence interval; CVC, central venous catheter.

**TABLE 4** CRI and CRBSI

| | CRI | | | | | CRBSI | |
|---|---|---|---|---|---|---|---|
| | No | Yes | Multivariable analysis | | | No | Yes |
| Independent variable | n = 412 | n = 45 | OR | 95% CI | *P*-value | n = 109 | n = 15 |
| Age | 60 (16-93) | 59 (18-83) | 1.01 | 0.99-1.03 | .375 | 59 (16-92) | 60 (18-83) |
| Male gender | 210 (51) | 28 (62) | 1.56 | 0.79-3.10 | .188 | 64 (59) | 11 (73) |
| Days with catheter | 13 (1-144) | 14 (4-99) | 1.01 | 0.99-1.03 | .524 | 11 (1-113) | 18 (6-41) |
| Site of insertion | | | | | | | |
| Jugular vein | 243 (89) | 30 (11) | — | — | — | 71 (65) | 8 (53) |
| Subclavian vein | 145 (93) | 11 (7) | 0.82 | 0.35-1.90 | .641 | 32 (29) | 5 (33) |
| Femoral vein | 9 (90) | 1 (10) | 0.70 | 0.08-5.93 | .747 | 3 (3) | 1 (7) |
| Number of catheter lumens | — | — | 1.63 | 1.11-2.39 | .013 | — | — |
| CHC vs CVC | 49 (89) | 6 (11) | 1.42 | 0.53-3.79 | .495 | 11 (10) | 1 (7) |
| After bundle | 208 (51) | 15 (33) | 0.46 | 0.23-0.92 | .029 | 59 (54.1) | 6 (40) |

*Note:* Data are presented as median (range) or number (percentage). "Bundle" refers to the hygiene bundle introduced in January 2012.
Abbreviations: CHC, central hemodialysis catheter; CRBSI, catheter-related bloodstream infection; CRI, catheter-related infection; CI, confidence interval; CVC, central venous catheter; OR, odds ratio.

possible, and removing unnecessary catheters. The hygiene insertion bundle implemented during this study was similar (se Appendix S1) but also included washing of the insertion site twice with 0.5% chlorhexidine in 70% alcohol, placing a clean sheet under the patient before insertion, and giving the assistant responsibility for compliance with the bundle´s use. In the study by Pronovost et al,[12] there was no description of the insertion routines prior to the study intervention. Given that this study was performed a few years after the study by Pronovost et al and that our department had already embraced the advantages of good insertion hygiene, it is reasonable to assume that even though existing hygiene insertion routines are acceptable, the additional simple hygiene precautions described in this study may further prevent CRIs.

In the last 20 years, CRI and CRBSI incidence has been globally reduced, but the burden of CRI is still substantial; increasing costs, hospital stays and possibly mortality.[1,18,19] The efficiency of bundles reducing CRBSI has been validated in various trials.[10-12,19] In a European study by Van der Kooi et al[10] the CRBSI incidence was reduced from 2.4/1000 to 0.9/1000 catheter days. In the study by Pronovost et al[12] (Michigan, United States) the CRBSI incidence was reduced from 7.7/1000 to 1.4/1000 catheter days. A study from the United Kingdom by Longmate et al[11] showed a reduction in CRBSI from 3.4/1000 to 0/1000 catheter days after implementing hygiene bundles. Notably, the incidence and reduction in CRBSI varies markedly between centers internationally and cannot always be compared as they study different patient populations and different definitions of CVC infection are used (CRI, CRBSI or central line associated infection [CLABSI]).[1,4,5,20,21] Scandinavian data on both CRI/CRBSI incidence and the efficiency of bundles are scarce. This study confirms the low incidence of CRI and CRBSI in two other Scandinavian single-center studies from another regional hospital in Sweden.[5,22]

The micro-organisms found in this study are similar to those previously reported.[8,23] Notably, there were no methicillin-resistant *S. aureus* or vancomycin-resistant Enterococci isolates, which reflects the low prevalence of these bacteria in Sweden. The emergence of multiresistant bacteria in hospital associated infections are otherwise substantial in Europe, and in some countries multiresistant bacteria constitute up to 30.2% of CRBSI pathogens.[24-26] The number of lumens was independently associated with CRI and catheter colonization in our study. Each added CVC lumen increased the odds of CRI approximately 63%. The increasing area of catheter material where microbes may adhere and the number of ports where microbes may be injected could explain this difference to some extent. Our results are consistent with some prior studies[23,27,28] although the results in the literature are conflicting.[29] It should be noted that no large study, adjusting for comorbidities and the degree of sickness, has confirmed these findings and that the multivariable regression model used in this study did not adjust for the degree of sickness or comorbidities. Studies on more homogenous groups of patients have indicated benefits from choosing single-lumen over multiple-lumen catheters in varied patient populations, including critically ill and cancer patients.[23,27,28] Nevertheless, we conclude that even though the evidence is scarce, multiple-lumen catheters should be used restrictively and the need for extra lumens should be carefully evaluated before insertion.

It has been demonstrated that the time with CVC is associated with CRI.[21] This was not the case in this study, which may be explained by the adherence to routines, including the active removal of unnecessary catheters. This was demonstrated in a Scandinavian study by Hammarskjöld et al, in which only a weak association (OR 1.002) with time was observed and was explained by strong adherence to the use of bundles, including active and early removal of catheters that were no longer necessary.[5] Nevertheless, these

findings have to be confirmed in larger trials, evaluating similar patient population and hygiene routines.

In this study, catheters placed in the subclavian vein were associated with less risk of colonization, but not for CRI in a multivariable logistic regression analysis. The preferable choice of the subclavian vein has recently been evaluated in a large trial comparing the jugular, femoral, and subclavian sites; the subclavian site conferred a stronger benefit than the alternatives.[4] At our institution, the subclavian vein was the primary choice for sicker and immune-compromised patients (eg, patients receiving chemotherapy), which may explain why the subclavian route was not associated with lower risk for CRI than the standard, internal jugular route.

## 5 | LIMITATIONS OF THE STUDY

We recognize that this study has limitations due to its retrospective nature. First, due to low incidence of outcomes, all potential risk factors involved in the development of CRI and catheter colonization, could not be included in the multivariable regression analyses. For example, other investigators have observed patients with immunosuppression, medical diagnosis at admission, parenteral nutrition, and trauma to be associated with CRI.[21,28] Although the instructions for taking peripheral blood cultures were carefully implemented when CRI was suspected, this was often not done (in 333 cases (73%)), possibly underestimating CRBSI incidence. In critically ill patients, it has previously been described that patients can fulfill the SIRS criteria and still not have CRI. This may overestimate the CRI incidence and make differentiation between colonization and CRI difficult. The implemented hygiene insertion bundle was widely distributed in the department, and the CVC-insertion assistants noticed that the staff was highly aware of the new hygiene insertion bundle. Nevertheless, individual compliance with guidelines could not be evaluated. Furthermore, the findings are dependent on other important factors to be unchanged between the year before and the year after the implementation of the bundle´s. Although, the authors investigated this issue carefully and found that no other important factor was changed either in the insertion routine or in the maintenance of CVCs, this possible time-dependent bias should be noted. This study evaluates a hygiene insertion bundle implemented in January 2012. Preserved low incidence of CRI/CRBSI to date cannot be guaranteed.

## 6 | CONCLUSION

The incidence of CRI and CRBSI in this Scandinavian cohort was low. The implementation of a simple hygiene insertion bundle was associated with decreased incidence of catheter-tip colonization and CRI, and large-bore catheters with multiple lumens were associated with increased incidence of catheter-tip colonization and CRI. These data further corroborate the evidence that hygiene insertion bundles should be used and that multiple-lumen catheters should be used restrictively.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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RESEARCH ARTICLE

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# Central venous catheter-related complications in hematologic patients: An observational study

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## Abstract

**Background:** The frequency of central venous catheter (CVC)-related complications in hematologic patients has previously been studied but some uncertainty remains. Therefore, this observational cohort study was designed primarily to investigate mechanical and infectious complications related to CVC insertion in hematologic patients and secondarily to identify factors associated with these complications.

**Methods:** Documented data on CVC insertions in all adult hematologic patients who received a CVC from 2013 to 2019 at a University Hospital in Sweden were retrospectively collected.

**Results:** A total of 589 CVC insertions in 387 patients were included. The prevalence of moderate and severe mechanical complications, predominantly comprising grades 2–4 bleeding, was 11%. Preprocedural coagulopathy, number of needle passes, and arterial puncture were all independently associated with grades 2–4 bleeding. The incidence of suspected catheter-related infections (sCRI) was 3.7/1000 catheter days. Higher body mass index and male gender were independently associated with sCRI.

**Conclusions:** Patients with hematologic malignancies have a high risk of both grades 2–4 bleeding and sCRI after CVC insertion. This underlines the importance of optimizing the conditions at the insertion and also of daily inspections, evaluation of future needs, and extra precautions to avoid sCRI in these susceptible patients.

### Editorial Comment

This retrospective cohort analysis in hematologic patients in a university hospital receiving a central vein catheter as part of their treatment describes related mechanical and infectious complications. This confirms that complications occur, and this type of cohort is vulnerable and worthy of extra care to try to limit events and morbidity related to them.

## 1 | INTRODUCTION

Central venous catheters (CVCs) are routinely placed in hematologic patients, providing an access point for drug administration, laboratory testing, and parenteral nutrition. These patients are frequently pancytopenic and have been reported to be at higher risk for catheter-related complications such as bleeding and catheter-related infections (CRIs).[1,2] In the last decade, routine improvements of CVC insertion and management, such as ultrasound-guided catheter placement and the introduction of hygiene bundles, have been

implemented worldwide.[3,4] These measurements have been shown to decrease the incidence of CVC-associated complications and overall hospital costs.[1,3,5] A few studies have been published outlining mechanical and infectious CVC-related complications in hematologic patients. However, those studies were either small, or the CVC insertion in the studies was mainly performed without ultrasound guidance and included only tunneled silicone CVCs.[2,6] Therefore, we designed this retrospective observational study with the primary aim of investigating the prevalence and incidence of CVC-related mechanical and infectious complications after insertion of nontunneled, noncoated CVCs in a cohort of hematologic patients. The secondary aim was to explore factors potentially associated with CVC complications. We hypothesized that hematologic patients have a high risk of both mechanical and infectious complications after CVC insertions and that several risk factors for complications can be identified.

## 2 | METHODS

This study was approved by the Swedish Ethical Review Authority (dnr 2014/916 and 2018/866). The requirement for written informed consent was waived. The study was carried out at the Department of Intensive and Perioperative Care at Skåne University Hospital, Lund, Sweden. The manuscript was prepared according to the STROBE guidelines for observational studies.[7] Details on the study methods are presented in Figure 1. The subclavian vein was the preferred site of CVC insertion, since the patients were considered at high risk of infection and because the CVC was expected to remain in situ for more than a week.

### 2.1 | Outcomes

The primary outcomes were moderate and severe mechanical complications and infectious complications.

Mechanical complications included bleeding complications, arterial puncture, pneumothorax, arrhythmia, and nerve injury/rhizopathy within 48 h of insertion. Severity of mechanical complication was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)[8] and further classified into mild, moderate, and severe as demonstrated in Table 1.

Infectious complications were defined in accordance with recent publications based on the definitions used by the Centers for Disease Control and Prevention.[9–11]

#### 2.1.1 | Suspected catheter-related infection (sCRI)

Either a positive catheter tip culture or a positive peripheral blood culture together with at least two of three systemic inflammatory response syndrome (SIRS) criteria at the removal of the CVC (fever >38°C or <36°C, heart rate > 90 beats per min, respiratory rate > 20 breaths per min). Leukocytopenia or leukocytosis was not considered an SIRS criterion because hematologic patients already have disturbed leukocyte counts due to reasons other than infections.

*and*

no likely infectious cause other than the catheter.

*and*

no likely *noninfectious* cause, for example, drug- or transfusion-related adverse reaction, venous thromboembolism, or mucositis.

*or*

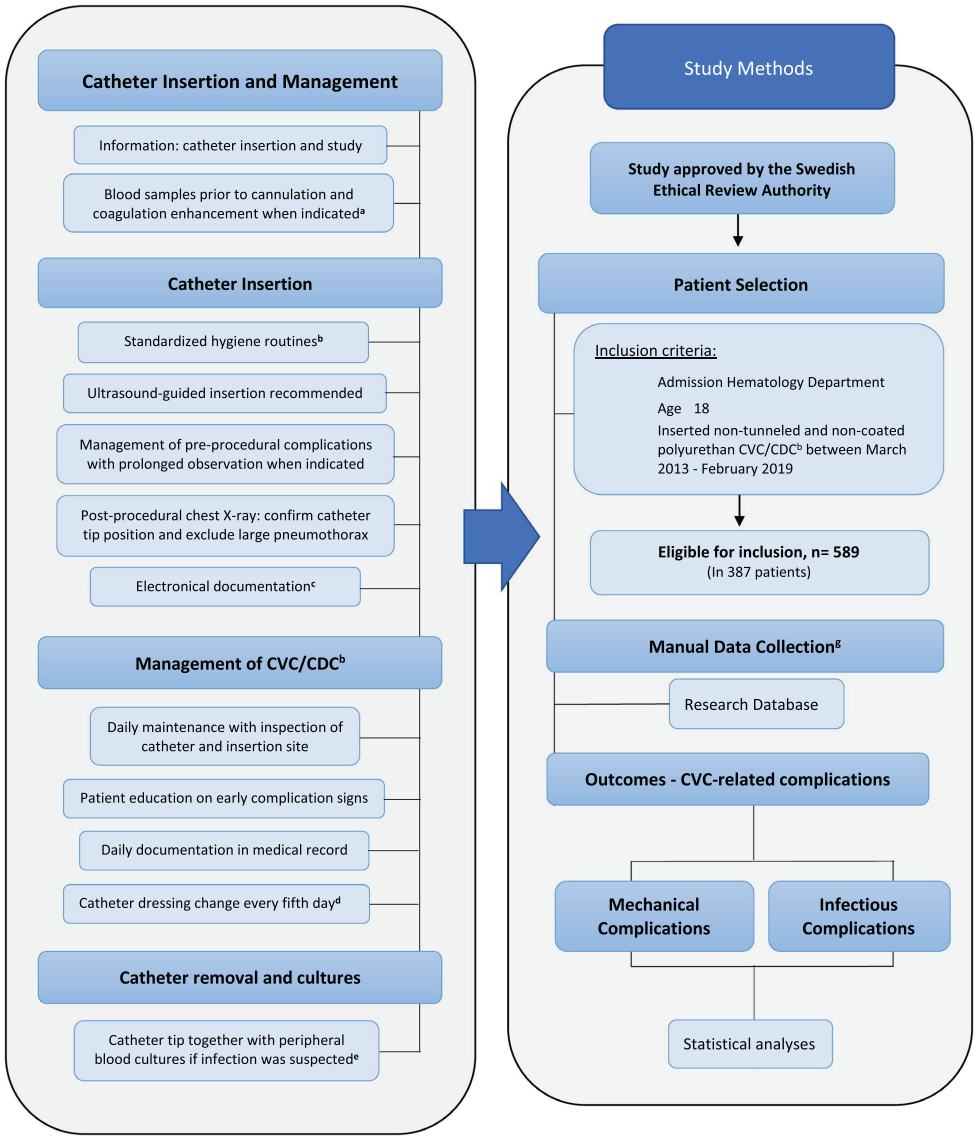
local inflammation and signs of infection.

Catheter-related bloodstream infection (CRBSI): Growth of the same microorganism on both the catheter tip and in peripheral blood (within 48 h prior to the removal of the CVC) together, with at least two of four SIRS criteria (three in the current study) with no likely explanation for a cause other than the catheter.

### 2.2 | Statistical analyses

The sample size was based on the number of available patients during the study period. Results were expressed as a median (interquartile range) for continuous variables and a number (percentage) for categorical variables. When comparing binary variables, the chi-square

**FIGURE 1** Flow charts describing the study methods. All inserted catheters together with the daily inspections and their management was documented in the patient's electronical file. Detailed data on catheter insertion and management, together with all microbiological data, were manually extracted and analyzed. Every patient had the right to opt out from the study. [a] Blood samples were obtained within 24 h prior to cannulation, and prophylactic coagulation enhancement was considered in patients with preprocedural coagulopathy, defined as platelet count $<50 \times 10^9$/L, prothrombin time (PT-INR) > 1.8, or APTT > 43 s (equal to more than 1.3× upper normal value). [b]CDC, central dialysis catheter; CVC, central venous catheter. Management of catheters is described in reference [13] (Thorarinsdottir et al.). [c]All catheter insertions and any preprocedural complication were documented in the electronic medical chart using a standardized CVC insertion template described in reference [12] (Björkander et al.). [d]Nonantimicrobial transparent catheter dressings (Tegaderm™; 3M) were changed every fifth day or more frequently if needed. Once the old dressing was removed, the insertion site was cleaned with 0.9% saline solution and washed with 0.5% chlorhexidine/70% alcohol (SCHA) solution. [e]The CVCs were removed after site treatment with 0.5% chlorhexidine/70% alcohol (SCHA) solution and the distal 5 cm of the catheter was cut and submerged in a culture tub, which was sonicated in 10 ml of broth. 0.1 ml of the broth was quantitatively cultured on blood agar plates. Growth of $>10^2$ CFU/catheter was considered significant colonization. The BACT/ALERT system (BioMérieux) was used for blood cultures. All bottles were incubated until microbial growth was detected or for a maximum of 5 days. [g]Electronic medical records of all patients eligible for inclusion were manually reviewed, and relevant data were extracted and entered in the research database (Microsoft Access, version 2016)




test was applied. To evaluate the associations between independent variables and grades 2–4 bleeding and CRI, univariable and multivariable logistic regression analyses were applied. The selection of independent variables in the regression analyses was based on results from previous studies[12,13] and the significant results in the univariate analysis were further analyzed in a multivariable analysis. The Hosmer-Lemeshow test was used to test the goodness of fit for multivariable testing. $p < .05$ was considered significant and all tests were two-tailed. All analyses were performed using SPSS 25 (SPSS Inc/IBM).

## 3 | RESULTS

Baseline characteristics of patients and CVCs are presented in Table 2. In summary, a total of 589 catheter insertions were

**TABLE 1** Mechanical complications classified according to their severity, based on the terms defined by the Common Terminology Criteria for Adverse Events[8]

| Severity of mechanical complication | Complications |
|---|---|
| Mild | Bleeding grade 1[a] |
| | Arrhythmia grades 1–2[b] |
| | Transient rhizopathy |
| Moderate | Bleeding grade 2[c] |
| Severe | Bleeding grades 3–4[d] |
| | Pneumothorax |
| | Arrhythmia grades 3–4[e] |
| | Persistent rhizopathy |

[a]Slight oozing from the insertion site not requiring intervention.
[b]Transient arrhythmia not requiring intervention.
[c]Bleeding requiring prolonged external compression.
[d]Grade 3 bleeding requiring transfusions or subacute invasive measures. Grade 4 bleeding is defined as a life-threatening condition in need of urgent intervention.
[e]Grade 3: Significant arrhythmia in need of medical intervention. Grade 4: significant arrhythmia causing hemodynamic compromise.

**TABLE 2** Characteristics of central venous catheters and patients[a]

| | |
|---|---|
| *Catheter characteristics* | |
| Central venous catheters inserted, total | 589 (100) |
| Days with catheter | 25 [9.0–43] |
| Type of catheter | |
| CVC | 564 (96) |
| Central dialysis catheter | 25 (4.2) |
| Site of insertion | |
| Subclavian vein | 433 (74) |
| Internal jugular vein | 150 (25) |
| Femoral vein | 5 (0.8) |
| Missing | 1 (0.2) |
| Number of lumens | |
| 1 | 469 (80) |
| 2 | 33 (6.0) |
| 3 | 12 (2.0) |
| 4 | 6 (1.0) |
| 5 | 14 (2.0) |
| Central dialysis catheter | 25 (4.0) |
| Missing | 30 (5.0) |
| Number of needle passes | |
| 1 | 385 (66) |
| 2 | 85 (14) |
| 3 | 38 (6.0) |
| >4 | 26 (4.0) |
| Missing | 55 (10) |
| Ultrasound guidance | 415 (70) |
| Reason for removal | |
| Ceased usage | 373 (63) |
| Suspected or confirmed infection | 89 (15) |
| Patient death | 49 (8.0) |
| Catheter malfunction | 10 (2.0) |
| Accidental removal | 10 (2.0) |
| Mispositioning | 11 (2.0) |
| Confirmed venous thrombosis | 3 (0.5) |
| Mechanical complication (bleeding) | 2 (0.5) |
| Missing | 42 (7.0) |
| Preprocedural coagulopathy[b] | 219 (37) |
| Missing data | 20 (3.4) |
| *Patient characteristics* | |
| Patients, total | 387 |
| Age, years | 57 [41–68] |
| Male gender | 256 (66) |
| Body mass index (BMI) | 25 [23–29] |
| Body temperature at time of catheter insertion (°C) | 37.1 [36.6–37.4] |
| Hepatosplenomegaly[c] | 124 (32) |
| Diagnosis | |
| Acute myeloid leukemia (AML) | 153 (40) |
| Acute lymphoblastic leukemia (ALL) | 50 (13) |
| Lymphoproliferative neoplasms/lymphoma | 48 (12) |
| Myeloma | 34 (9.0) |
| Acute promyelocytic leukemia (APL)[d] | 22 (5.0) |
| Myelodysplastic syndrome (MDS) | 15 (4.0) |
| Myeloproliferative neoplasms (MPN) | 12 (3.0) |
| Other[e] | 53 (14) |

[a]Data are presented as median IQR [Q1–Q3] or number (percentage).
[b]Number of cases with coagulopathy defined as ≥1 abnormal preprocedural blood coagulation tests, that is, platelet count $<50 \times 10^9$/L, PT-INR >1.8, or APTT (activated partial thromboplastin time) >43 s which equals more than 1.3× the normal value.
[c]Spleen and liver status on day of catheter insertion based on estimations using either abdominal CT scan or ultrasound (performed in 102/124 cases) or documented clinical examination at admission. There were no splenectomized patients.
[d]APL is a subgroup of AML with tendency toward more aggressive coagulopathy.
[e]Other diagnoses included amyloidosis, demyelinating polyneuropathies, Ewing sarcoma, idiopathic thrombocytopenic purpura, monoclonal gammopathy, multiple sclerosis, necrobiotic xanthogranuloma, plasmocytoma, scleroderma, and thrombotic thrombocytopenic purpura.

performed in 387 patients, during the study period of 71 months. The majority of catheters inserted were single lumen 469/589 (80%) and most catheters were inserted in the subclavian vein 433/589 (74%). Of all patients ($n$ = 387), 256 (66%) were men and the most common diagnosis was acute myeloid leukemia 153/387 (40%).

### 3.1 | Outcomes

Detailed data on outcomes per insertion site are presented in Table 3.

### 3.2 | Mechanical complications

In 64/589 (11%) of all insertions, a moderate 50/589 (8.5%) or severe 14/589 (2.4%) mechanical complication occurred. Ultrasonography was used in the majority of insertions that resulted in grades 2–4 bleeding 46/61 (75%) but did not show statistical significance in the univariable logistic regression analysis and was therefore not included in the multivariate analysis.

Arterial punctures occurred in 18/589 (3.1%) insertions, where 4/18 (22%) resulted in grades 3–4 bleeding and 4/18 (22%) in grade 2 bleeding. Out of all grades 2–4 bleedings, 8/61 (13%) occurred after an arterial puncture. Detailed data on preprocedural coagulopathy and correction of hemostasis is described in Figure 2 and File S1.

In the multivariable logistic regression analyses for both grades 2–4 bleeding and sCRI, the goodness of fit showed a valid chi-square value ($p > .05$) for all outcomes. Detailed results of the uni- and multivariable regression analyses on grades 2–4 bleeding are shown in Tables 4 and 5. The results of the univariable regression analyses were used to identify variables for the multivariable analyses. Corrected or uncorrected preprocedural coagulopathy ($p < .001$), number of needle passes ($p = .008$), and arterial puncture ($p = .004$) were all independently associated with grades 2–4 bleeding in the multivariable analysis.

Three cases (0.5%) presented with a pneumothorax on the same side as the catheter insertion, all verified with a plain chest X-ray. In 2/3 cases (67%), ultrasound-guided insertion was applied.

### 3.3 | Infectious complications

A detailed description of each case with sCRI can be seen in File S2. In summary, 69 patients were diagnosed with sCRI (12%), yielding an incidence of 3.7 sCRI/1000 catheter days during the study period. The incidence of sCRI in catheters placed in the subclavian vein was 3.3/1000 catheter days and 5.6/1000 catheter days in the internal jugular vein. There was no difference in the incidence of sCRI after subclavian compared with internal jugular insertions ($p = .58$). Out of all 69 sCRI, 12 were further classified as CRBSI, yielding a prevalence of 2.0% and an incidence of 0.64 CRBSI/1000 catheter days (Table 3).

Out of all 589 insertions, 373 (63%) cases were given antibiotics 24 h prior to catheter insertion. Most frequently, patients were administered a one-time prophylactic dose of Rifampicin (47%). Of the 69 cases with sCRI, 61 (88%) had antibiotic treatment at insertion.

In 54 out of all 69 (78%) cases with sCRI, the responsible pathogen was identified. In the other cases (15/69), the classification of sCRI was based on positive cultures described in the follow-up notes at the hematology department.

Detailed results of the uni- and multivariable regression analyses on sCRI are shown in Tables 4 and 5. High BMI ($p = .031$) and male gender ($p = .002$) were both independently associated with sCRI in the multivariable analysis.

## 4 | DISCUSSION

This retrospective observational study on nontunneled and noncoated CVC insertions in hematologic patients demonstrated an overall high prevalence of moderate to severe mechanical complications and a high sCRI prevalence (12%) with an sCRI incidence of 3.7 sCRI/1000 catheter days. These results are compared with previously published studies on hematologic patients[2,6] and higher than earlier reports on general cohorts[12,13] and should therefore be carefully considered before cannulation of hematology patients.

### 4.1 | Mechanical complications

In a previous study on CVC insertions in an unselected cohort of 10,949 patients >16 years of age, from the same hospital as the present study, we reported a prevalence of mechanical complications of 1.1%.[12] In other studies in unselected adult cohorts frequencies of mechanical complications are reported with a wide interval of 1.1% and 7.6%, mostly dependent on different definitions of mechanical complications.[9] In hematologic patients, Dix et al. prospectively studied 174 nontunneled CVC insertions and reported immediate mechanical complications in 7.5% of cases,[2] whereas Morano et al. demonstrated mechanical complications in 7.2% of hematology patients in a retrospective study on tunneled CVCs inserted.[6] These results should be compared with the prevalence of moderate and severe mechanical complications, occurring in 11% of cases, in the present study. However, it should also be noted that in the referred studies, bleeding complications were not graded nor defined according to their time of occurrence, which complicates the comparison with the present study.

Given that mechanical complications are common in hematologic patients, optimization of conditions at insertion is of utmost importance. One example of such optimization may be a routine preprocedural ultrasound scan to anticipate any insertion problem, such as an anatomically challenging positioning of the vein. Based on that information, the clinician can decide on any prophylactic pro-coagulative treatment. Although logistically challenging, this approach is appealing.

Ultrasound-guided technique was used in the majority of all catheter insertions (70%), however, in this study, its use was not associated with reduced risk for mechanical complications. Previous studies have convincingly demonstrated that real-time ultrasound reduces the risk for mechanical complications.[5] The lack of shown usefulness of ultrasound in the present study may be explained by

**TABLE 3** Outcomes per site of insertion[a]

| Outcome | Subclavian *n* = 433 | Internal jugular *n* = 150 | Femoral *n* = 5 | Total *n* = 589 |
|---|---|---|---|---|
| *Mechanical complications* | | | | |
| Bleeding grade[b] | | | | |
| 1 | 77 (18) | 12 (8.0) | 0 (0) | 89 (15) |
| 2 | 33 (7.6) | 16 (11) | 1 (20) | 50 (8.5) |
| 3 | 8 (1.8) | 0 (0) | 0 (0) | 8 (1.4) |
| 4 | 2 (0.5) | 1 (0.7) | 0 (0) | 3 (0.5) |
| Aggregated grades 2–4 | 43 (10) | 17 (11) | 1 (20) | 61 (10) |
| Pneumothorax | 3 (0.7) | 0 (0) | 0 (0) | 3 (0.5) |
| Arrythmias | | | | |
| Mild | 3 (0.7) | 0 (0) | 0 (0) | 3 (0.5) |
| Moderate–severe | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Nerve injury | | | | |
| Mild | 4 (0.9) | 1 (0.7) | 0 (0) | 5 (0.8) |
| Moderate–severe | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Prevalence of mechanical complications | | | | |
| Mild mechanical complications[c] | 84 (19) | 13 (8.7) | 0 (0) | 97 (16) |
| Moderate mechanical complications[d] | 33 (7.6) | 16 (11) | 1 (20) | 50 (8.5) |
| Severe mechanical complications[e] | 13 (3.0) | 1 (0.7) | 0 (0) | 14 (2.4) |
| *Infectious complications*[f] | | | | |
| Days with catheter, total | 16077 | 2692 | 40 | 18814 |
| Catheter days | 28 [17–53] | 13 [5–27] | 7 [5–12] | 25 [9–43] |
| sCRI prevalence, *n* (%) | 53 (12) | 15 (10) | 0 (0) | 69 (12)[g] |
| sCRI incidence/1000 catheter days | 3.3 | 5.6 | 0 | 3.7 |
| CRBSI prevalence, *n* (%) | 9 (2.0) | 3 (2.0) | 0 (0) | 12 (2.0) |
| CRBSI incidence/1000 catheter days | 0.56 | 1.11 | 0 | 0.64 |

[a]Data presented as numbers (%) or median IQR [Q1–Q3].
[b]Bleeding observed within the first 48 h after insertion.
[c]Mild mechanical complications included bleeding grade 1, arrhythmia grades 1–2, and transient rhizopathy.
[d]Moderate mechanical complications included bleeding grade 2.
[e]Severe mechanical complications included grades 3–4 bleeding and pneumothorax.
[f]Presented as infection incidence (%) and infection rate/1000 catheter days.
[g]Data on the location of one infected catheter are missing.

inconsistent use at the discretion of the inserting operator and not always in real time as in previous studies.

The number of needle passes and arterial punctures was associated with grades 2–4 bleeding. Both variables have previously been described as risk factors for mechanical complications in general cohorts.[2,12,14–16] Moreover, preprocedural coagulopathy was associated with grades 2–4 bleeding. In the majority of these bleedings, the patients were preprocedurally given platelets (Tables 4 and 5; Figure 2; File S1), yet coagulopathy was still correlated with moderate to severe bleeding. This observation is described by van der Weerdt et al., who noted no beneficial effect from prophylactic platelet administration.[14] One possible explanation for these findings is that the clinician may be more likely to give platelet transfusions to more compromised patients. Further, in the present study, posttransfusion platelet count was generally not controlled, which implies that patients with low numbers of preprocedural platelets may not have reached the recommended platelet count of $50 \times 10^9$/L. Moreover, both the present study and the study by van der et al. rely on retrospective observations with a risk of bias.

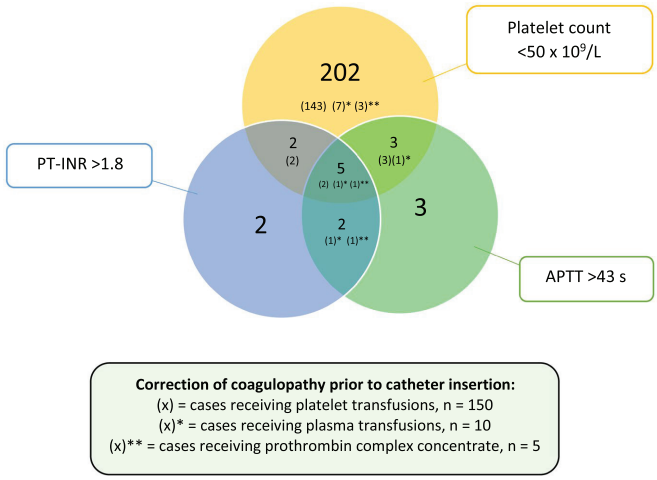



**FIGURE 2** The Venn Diagram shows the relationship between preprocedural coagulation defects and the correction of hemostasis. The total number of isolated coagulopathies are presented separately, whereas the number of cases receiving any pro-coagulative treatment before insertion are presented within brackets, as explained in the figure above. Two hundred and two cases presented isolated platelet count $<50 \times 10^9$ L, two cases presented isolated PT-INR > 1.8, and three cases had an isolated APTT > 43 s. For more details on the preprocedural correction of coagulopathy, see File S1. APTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio.

As CVCs inserted in the subclavian vein have been reported to result in less infectious complications,[17] clinicians experience less infusion disruptions and the patients probably encounter less discomfort, this was the standard site of insertion. However, 13 of totally 14 severe mechanical complications occurred after subclavian insertion. Even though 433 cases with subclavian insertion and only 155 cases with insertions in other veins were studied, this supports previous studies showing a higher risk for mechanical complications after subclavian insertions.[17]

## 4.2 | Infectious complications

Our observation of sCRI incidence (3.7/1000 catheter days) is in the range of infection rates previously reported, where the CRI and CRBSI incidences in similar cohorts as the present study ranged between 1.3 and 7.6/1000 catheter days.[2,6,18] However, it should be highlighted that the type of CVCs included and the definition of CRI vary between these studies and the present one, which complicates the comparison. As postulated by Tomlinson et al. in a systematic review on 191 studies reporting CRIs, uniformity of definition is lacking and some studies even fail to cite or report a definition.[10] Moreover, the term CRI and central line-associated bloodstream infection (CLABSI) are frequently interchanged. By definition, CLABSI or CABSI (catheter-associated blood stream infection) occurs when there is the growth of a microorganism in blood cultures with a CVC present at the time of infection or within 48 h prior to the development of infection, with no likely explanation for a cause other than the catheter.[10] Since these terms differ, a more recent definition—suspected CRI—used in this manuscript, has been suggested in recent expert consensus-based clinical practice guidelines.[11] Many use CRBSI as a measure of CRI. However, as pointed out by others, one problem with the strict CRBSI definition in hematologic patients is that the majority of patients are treated with intravenous antibiotics both prior to catheter insertion and throughout its usage.[19] As many organisms in significant CRIs are hidden from antibiotics in a biofilm on the catheter but killed by antibiotics if released into the bloodstream, many blood cultures could yield false-negative results.[20] Therefore, we argue that a broader definition such as sCRI, despite lowering the specificity, increases the sensitivity for CRIs.

In a recent report from our group, Thorarinsdottir et al. studied CRIs in a general patient cohort, after the implementation of hygiene bundles, reported a CRI prevalence of 2.6% with an incidence of 1.9/1000 catheter days.[13] In, the present study on hematologic patients the prevalence was 12% and the incidence 3.7/1000 catheter days. These higher numbers underline the importance of daily inspections, evaluation of future needs, and extra precautions to avoid CRI in these susceptible hematologic patients.

Higher BMI and male gender were associated with sCRI in this cohort. Obesity has previously been identified as a risk factor for sCRI in critically ill patients.[21,22] In a prospective study on nonhematologic patients, Dossett et al. suggested that obese patients have an increased risk of sCRI because of longer severity-adjusted ICU stays, increasing their risk of nosocomial infections.[22] Another theory is that it could be due to increased perspiration, as bandages are more

**TABLE 4** Univariable regression analyses for each outcome variables. Independent variables were chosen based on previous studies.[12,13] Highlighted variables were further analyzed in a multivariable regression analysis (Table 5)

| | Early grades 2–4 bleeding, *n* = 61 | | | | |
|---|---|---|---|---|---|
| | No | Yes | Univariable analyses[e] | | |
| **Independent variables** | ***n* = 528** | ***n* = 61** | **OR** | **95% CI** | ***p* value** |
| Body mass index | 26 [23–29] | 26 [23–29] | 0.998 | 0.945–1.054 | .933 |
| Male gender | 233 (44) | 23 (38) | 1.305 | 0.756–2.252 | .339 |
| Hepatosplenomegaly | 486 (92) | 59 (96) | 2.549 | 0.602–10.804 | .204 |
| Operator experience >5 year | 355 (67) | 43 (70) | 1.237 | 0.644–2.377 | .523 |
| Male operator | 406 (77) | 49 (80) | 1.227 | 0.632–2.381 | .545 |
| Number of needle passes[a] | 1 [1–2] | 1 [1–2] | 1.317 | 1.070–1.620 | **.009** |
| *Site of insertion* | | | | | |
| Subclavian vein | 390 (74) | 43 (70) | 0.845 | 0.472–1.515 | .572 |
| Internal jugular vein | 133 (25) | 17 (28) | 1.147 | 0.634–2.077 | .649 |
| Femoral vein | 4 (8.0) | 1 (2.0) | 2.183 | 0.240–19.854 | .488 |
| Left sided CVC insertion | 297 (57) | 34 (56) | 0.971 | 0.569–1.656 | .914 |
| Number of lumens | 1 [1–1] | 1 [1–1] | 0.975 | 0.779–1.220 | .823 |
| Ultrasound guidance | 369 (70) | 46 (75) | 1.321 | 0.717–2.436 | .372 |
| Arterial puncture | 10 (2.0) | 8 (13) | 7.819 | 2.959–20.661 | **.000** |
| Coagulopathy[b] | 171 (32) | 36 (59) | 2.931 | 1.704–5.039 | **.000** |
| Diagnosis AML[c] at CVC[d] insertion | 260 (49) | 28 (46) | 0.875 | 0.514–1.488 | .621 |
| | **Suspected catheter-related infections (sCRI), *n* = 69** | | | | |
| | No | Yes | Univariable analyses[e] | | |
| **Independent variables** | ***n* = 520** | ***n* = 69** | **OR** | **95% CI** | ***p* value** |
| Body mass index | 26 [23–29] | 27 [25–30] | 1.040 | 0.993–1.089 | **.097** |
| Male gender | 281 (54) | 52 (75) | 2.602 | 1.465–4.619 | **.001** |
| Total catheter days | 27 [13–47] | 28 [19–48] | 1.002 | 0.995–1.010 | .549 |
| Number of needle passes | 1 [1–2] | 1 [1–2] | 1.185 | 0.957–1.467 | .120 |
| *Site of insertion* | | | | | |
| Subclavian vein | 380 (73) | 53 (77) | 1.220 | 0.675–2.205 | .509 |
| Internal jugular vein | 135 (25) | 15 (22) | 0.792 | 0.433–1.450 | .450 |
| Number of lumens | 1 [1–1) | 1 [1–1] | 0.685 | 0.470–1.000 | **.050** |
| Arterial puncture | 16 (23) | 2 (3.0) | 0.940 | 0.212–4.180 | .936 |
| Bleeding[d] | 185 (36) | 30 (43) | 1.393 | 0.838–2.317 | .202 |
| Coagulopathy[b] | 187 (36) | 20 (29) | 0.707 | 0.408–1.226 | .217 |
| Diagnosis AML[c] at CVC insertion | 246 (48) | 42 (60) | 1.733 | 1.037–2.895 | **.036** |

Abbreviation: CVC, central venous catheter.

[a]Increased risk for grades 2–4 bleeding in insertions requiring more needle passes.

[b]Coagulopathy was defined as ≥1 abnormal preprocedural blood coagulation test, that is, platelet count $<50 \times 10^9$/L, PT-INR > 1.8, or APTT (activated partial thromboplastin time) >43 s, which equals more than 1.3× the normal value.

[c]Acute Myeloid Leukemia including APL (Acute Promyelocytic Leukemia), a subgroup of AML with tendency toward more aggressive coagulopathy.

[d]Early or late with the severity mild to severe.

[e]Data are presented as 95% Confidence Interval (CI) of Odds Ratio (OR).

prone to detach leading to a risk of wound infection.[23] Further studies are needed to determine the association between high BMI and sCRI in hematologic patients.

Reports on male gender being a risk factor for sCRI in hematologic patients are scarce but has been described as a risk factor for sCRI in nonselected patients.[24] However, in one randomized

**TABLE 5** Multivariable regression analysis based on the results from the univariable regression analysis (Table 4) and on risk factors described in previous studies.[12,13]

| | Early grades 2–4 Bleedings, $n = 61$ | | |
|---|---|---|---|
| | Multivariable analyses[b] | | |
| **Independent variables** | **OR** | **95% CI** | ***p* value** |
| Coagulopathy[a] | 4.698 | 2.385–9.253 | **<.001** |
| Subclavian vein | 0.691 | 0.2707–1.724 | .428 |
| Number of lumens | 0.852 | 0.607–1.196 | .355 |
| Operator experience > 5 years | 1.293 | 0.615–2.717 | .497 |
| Number of needle passes | 1.405 | 1.095–1.804 | **.008** |
| Arterial puncture | 6.362 | 1.817–22.28 | **.004** |
| | **Suspected catheter-related infections (sCRI), $n = 69$** | | |
| | Multivariable analyses[b] | | |
| **Independent variables** | **OR** | **95% CI** | ***p* value** |
| Body Mass Index | 1.065 | 1.006–1.127 | **.031** |
| Male gender | 2.841 | 1.451–5.561 | **.002** |
| Total catheter days | 1.003 | 0.994–1.012 | .519 |
| Number of lumens | 0.710 | 0.455–1.110 | .133 |
| Number of needle passes | 1.223 | 0.973–1.538 | .085 |
| Diagnosis AML at CVC insertion | 1.743 | 0.953–3.189 | .071 |

Abbreviations: AML, acute myeloid leukemia; CVC, central venous catheter.

Statistically significant $p < .05$ values are highlighted in bold.

[a] Coagulopathy was defined as ≥1 abnormal preprocedural blood coagulation tests, that is, platelet count $<50 \times 10^9$/L, PT-INR > 1.8, or APTT (activated partial thromboplastin time) >43 s, which equals more than 1.3× normal value

[b] Data are presented with 95% Confidence Interval (CI) of Odds Ratio (OR).

controlled trial by Luft et al., investigating 219 hematologic patients receiving a CVC, the male gender was identified as an independent risk factor for skin colonization, potentially increasing the risk of catheter colonization.[25] Beard growth and shaving were observed to reduce adherence of wound dressing materials, suggesting an increased risk of bacterial contamination.

## 4.3 | Limitations

One of the major limitations of this study is its retrospective nature and the risk of missing data. Although there is a well-established routine for documenting catheter-related complications and securing infection-suspected catheter tips with simultaneous peripheral blood cultures in the studied departments, adherence to the routines cannot be guaranteed. Furthermore, the lack of uniformity in defining CRIs is an issue when reporting data. Moreover, this study was performed in a selected cohort with low incidences of some outcomes, making it impossible to include some risk factors in the multivariable regression analyses.

## 4.4 | Conclusions

Patients with hematologic malignancies have a high risk of both grades 2–4 bleeding and sCRI after CVC insertion.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

Data was collected and analysed mainly by MMR with contributions from HRT and TK. VL contributed with hematology specific data. Article was written by MMR, HRT, VL, MR and TK.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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# Paper III

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# Sustained low catheter related infection (CRI) incidence in an observational follow-up study of 9924 catheters using automated data scripts as quality assurance for central venous catheter (CVC) management

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SUMMARY

***Background:*** To maintain a low incidence of Catheter Related Infections (CRI) and Catheter Related Bloodstream Infections (CRBSI), continuous follow-up studies on catheter management are necessary. The aims of the present study were to investigate the incidence of catheter tip colonisation, CRI and CRBSI in the Region, to further explore the feasibility of automatic data collection and to investigate associations between independent variables and CRI.

***Methods:*** Data from electronic patient charts on all documented central venous catheter (CVC) insertions from multiple hospitals in southern Sweden, between March 2019 and August 2020, were automatically extracted. Multivariable regression analyses were used to identify associated risk factors.

***Results:*** In total, 9924 CVC insertions were included. The prevalence of CRI and CRBSI were 0.7% (*n = 74*) and 0.02% (*n = 20*) with incidences of 1.2/1000 catheter days and 0.3/1000 catheter days, respectively.

***Conclusions:*** We found a sustained low incidence of CRI and CRBSI in the Region. Catheter tips were less likely to be colonised when the subclavian route was used compared to the internal jugular route and male sex as well as increased number of catheter lumens were associated with both catheter tip colonisation and CRI. By using automated scripts, data extraction was efficient and feasible but also demonstrated that real-time quality assurance should be recommended, since this is superior to current standard.



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## Introduction

Over the last decades, improvements in the management of central venous catheters (CVCs) have been made to reduce catheter related infections (CRIs), including catheter related bloodstream infections (CRBSIs). However, CRI continues to be a problem, causing not only increased patient suffering but also a burden on healthcare economy with reports showing that one CRI can cost up to $32000 [1].

The view on CVC management and CRI prevention shifted in 2006 when Pronovost *et al*. described simple evidence-based interventions resulting in significant CRI reduction [2,3]. These interventions, also known as "insertion bundles" or "hygiene bundles", were implemented worldwide resulting in multiple reports on lowered CRI incidences [3]. In line with Pronovost's study, we introduced a simple hygiene insertion bundle in 2012 which was demonstrated effective as it reduced the incidence of CRI [4].

In contrast to the numerous publications reporting short-term low incidences of CRI after the introduction of various hygiene bundles [2,4,5], there are relatively few follow-up studies evaluating CRI incidences over time and focusing on the long-term effects of hygiene bundles. In the past decade, one quality improvement report published in 2011 by Batistella *et al*. [6] and one follow-up study from 2014 by Hammarskjöld *et al*. [7] both describe a sustained low catheter infection rate, six years after implementing new catheter insertion routines. In summary, these studies confirmed safe and effective implementation of new CVC-management strategies. However, more recent reports on CRI incidences with follow-up studies worldwide are scarce.

In parallel, modernisation of health records and patient data over the last decades has led to the development of electronic health record (EHR) systems comprised by valuable data used in epidemiological studies, such as the ones reporting catheter-related and other life-threatening infections [8,9]. Several recent studies have reported electronic surveillance systems and the use of data engines and search queries to monitor and report the management of CVCs, allowing tracking of compliance to CVC hygiene insertion bundles but also to monitor the infection and complication frequencies [8,10,11].

In an attempt to evaluate long-term effects of the hygiene insertion bundle introduced in 2012 at the current institution, we used automated script-based search in the EHR to conduct this multicenter observational follow-up study as a quality assurance measure of CRI over time. The primary aim of this study was to investigate the incidence of CRI and CRBSI using an automated script-based method in an unselected, large, cohort of patients with central venous access [4]. Secondarily, we aimed to identify associated risk factors for CRI.

## Methods

This study was approved by the Swedish Ethical Review Authority (dnr 2014/916 and 2018/866) and requirement for written informed consent was waived. The study was carried out at the Department of Intensive and Perioperative Care at Skåne University Hospital, Lund, Sweden. The manuscript was prepared according to the STROBE guidelines for observational studies.

All documented CVC insertions from ten different hospitals within the Scania Region (Region Skåne), Sweden, from March 2019 to August 2020 were eligible for inclusion. Exclusion criteria included patients under 8 years of age, missing insertion date or unknown insertion site. Peripherally inserted catheters (PICC-lines) and subcutaneous venous ports were not included as they were inserted using different techniques and different hygiene precautions.

### *CVC insertion, management, and removal*

CVC insertions were performed according to Regional guidelines, previously described[4, 12]. Some of the variables included in the template are described in Table I.

Catheter tips were only cultured if a CRI was suspected. CVCs were removed after site treatment with 0.5% chlorhexidine in 70% alcohol. The distal end of the CVC was submerged into a culture tube, and the distal 5cm was cut off. The tip was cultured using a semi-quantitative method where growth of >102 CFU/catheter tip was considered significant colonization [13,14]. Blood cultures taken between 0 - 48h after CVC removal were included in the data set. The automated BACT/ALERT®-system (BioMérieux, Marcy l'Etoile, France) was used and all cultures were incubated until microbial growth was detected or for a maximum of five days.

### *Data extraction*

By using an automated script-base search in the EHR (Melior, Cerner, North Kansas City (MO), USA), all documented CVC-insertion templated, during the study period, were extracted. Automatically extracted data was directly inserted into a compiled, encrypted database (Excel, version 10, Microsoft, Santa Rosa, USA), where each individual insertion was merged with matching microbiological data, laboratory values obtained within 48 hours prior to the CVC removal. All insertions with data fulfilling the exclusion criteria were removed from the database.

### *Outcomes and definitions*

The primary outcomes were defined according to the definitions used by Centers for Disease Control and Prevention (CDC) [15]. Catheter tip colonisation was defined as a positive tip culture in a patient where suspected catheter infection had led to removal of the CVC, regardless of clinical symptoms. CRI was defined as positive tip culture combined with two or more systemic inflammatory response syndrome (SIRS) criteria (fever >38 or <36 C°, respiratory rate >20 breaths per minute, heart rate >90 beats per minute or white blood cell count >12000/μL or <4000/μL) upon CVC removal and no likely explanation other than the catheter. The diagnosis of CRBSI required fulfillment of the CRI-criteria combined with a peripheral blood culture taken within 48h prior to CVC removal, with the same microorganism isolated in both cultures.

### *Statistics and analyses*

All analyses were performed using SPSS (version 28, IBM, New York, USA) using data from the original dataset. Results were expressed as a median [interquartile range] for continuous variables and a number (percentage) for categorical

**Table I**
Baseline variables for patients receiving a central venous catheter (CVC)[a]

| | Jugular vein n=8398 | Subclavian vein n=1330 | Femoral vein n=196 | All n=9924 |
|---|---|---|---|---|
| Number of patients | 5989 | 1176 | 169 | 6872 |
| Age, years | 70 [58–77] | 67 [53–75] | 60 [46–73] | 69 [57–76] |
| Sex, male | 5099 (61) | 828 (62) | 111 (57) | 6038 (61) |
| **Indication for CVC**[b] | | | | |
| Vessel irritating medication | 2797 (33) | 583 (44) | 72 (37) | 3452 (35) |
| Cardiac surgery | 2820 (34) | 277 (21) | 9 (5.0) | 3106 (31) |
| Parenteral nutrition | 1251 (15) | 196 (15) | 9 (5.0) | 1456 (15) |
| Haemodynamic monitoring | 2007 (24) | 259 (19) | 30 (15) | 2296 (23) |
| Peripheral venous access impossible | 1640 (20) | 339 (25) | 34 (17) | 2013 (20) |
| Blood sampling | 2436 (29) | 461 (35) | 45 (23) | 2942 (30) |
| Fluid resuscitation | 1496 (18) | 143 (11) | 43 (22) | 1682 (17) |
| Others | 1176 (14) | 101 (8.0) | 86 (44) | 1363 (14) |
| Missing | 174 (2.0) | 58 (4.0) | 6 (3.0) | 238 (2.0) |
| **Type of catheter** | | | | |
| Central Venous Catheter (CVC) | 8036 (96) | 1312 (99) | 142 (72) | 9490 (96) |
| Central Haemodialysis Catheter (CHC) | 362 (4.0) | 18 (1.0) | 54 (28) | 434 (4.0) |
| **Number of CVC lumen** | | | | |
| 1 | 2275 (27) | 353 (27) | 19 (9.0) | 2647 (27) |
| 2 | 1859 (22) | 311 (23) | 19 (9.0) | 2189 (22) |
| 3 | 2374 (28) | 380 (29) | 41 (22) | 2795 (28) |
| 4 | 587 (7.0) | 74 (5.0) | 5 (3.0) | 666 (7.0) |
| 5 | 799 (10) | 158 (12) | 46 (23) | 1003 (10) |
| Missing | 504 (6.0) | 54 (4.0) | 66 (34) | 624 (6.0) |
| **Anticoagulant treatment before insertion**[c] | | | | |
| No | 5441 (65) | 952 (72) | 128 (65) | 6521 (66) |
| Warfarin | 374 (4.0) | 43 (3.0) | 2 (1.0) | 419 (4.0) |
| Non-vitamin K Antagonist Oral Anticoagulants | 427 (5.0) | 45 (3.0) | 6 (3.0) | 478 (5.0) |
| Acetylsalicylic acid | 965 (11) | 132 (10) | 14 (7.0) | 1111 (11) |
| Low Molecular Weight Heparin | 709 (8.0) | 89 (7.0) | 18 (9.0) | 816 (8.0) |
| Other | 762 (9.0) | 103 (8.0) | 35 (18) | 900 (9.0) |
| **Procoagulant treatment before insertion**[d] | | | | |
| No | 7282 (87) | 1159 (87) | 153 (78) | 8594 (87) |
| Platelet transfusion | 110 (1.0) | 54 (4.0) | 8 (4.0) | 172 (2.0) |
| Activated prothrombin complex | 217 (3.0) | 18 (1.0) | 9 (5.0) | 244 (2.5) |
| Vitamin K | 82 (1.0) | 6 (0.5) | 5 (3.0) | 93 (1.0) |
| Fibrinogen | 35 (0.4) | 7 (0.5) | 3 (2.0) | 45 (0.5) |
| Plasma | 49 (0.5) | 7 (0.5) | 3 (2.0) | 59 (1.0) |
| Tranexamic acid | 71 (0.8) | 11 (1.0) | 4 (2.0) | 86 (1.0) |
| Desmopressin | 15 (0.2) | 3 (0.2) | 1 (1.0) | 19 (0.2) |
| Other | 753 (9.0) | 96 (7.0) | 27 (14) | 876 (9.0) |
| **Room for CVC-insertion** | | | | |
| Operating theatre | 4942 (59) | 395 (30) | 33 (17) | 5370 (54) |
| Intensive Care Unit | 2022 (24) | 469 (35) | 125 (64) | 2616 (26) |
| Room reserved for CVC-insertion | 902 (11) | 399 (30) | 22 (11) | 1323 (13) |
| General ward | 242 (3.0) | 40 (3.0) | 6 (3.0) | 288 (3.0) |
| Missing | 290 (3.0) | 27 (2.0) | 10 (5.0) | 327 (3.0) |
| **Department of admission at CVC insertion** | | | | |
| Surgical ward | 4504 (54) | 513 (39) | 28 (14) | 5045 (51) |
| Medical ward | 2282 (27) | 569 (43) | 59 (30) | 2910 (29) |
| Intensive Care Unit | 1335 (16) | 198 (15) | 91 (46) | 1624 (16) |
| Missing | 277 (3.0) | 50 (4.0) | 18 (9.0) | 345 (4.0) |
| **Number of skin punctures** | | | | |
| 1 | 6302 (75) | 1017 (76) | 149 (76) | 7468 (75) |
| 2 | 1333 (16) | 193 (15) | 20 (11) | 1546 (16) |
| 3 | 437 (5.0) | 67 (5.0) | 12 (6.0) | 516 (5.0) |
| 4 | 100 (1.0) | 21 (2.0) | 1 (0.5) | 122 (1.0) |
| 5 or more | 45 (0.5) | 12 (1.0) | 3 (1.0) | 60 (0.5) |

(*continued on next page*)

**Table I** (*continued*)

| | Jugular vein n=8398 | Subclavian vein n=1330 | Femoral vein n=196 | All n=9924 |
|---|---|---|---|---|
| Missing | 181 (2.5) | 20 (1.0) | 11 (5.5) | 212 (2.0) |
| **Number of vessel punctures** | | | | |
| 1 | 6584 (78) | 1130 (85) | 154 (79) | 7868 (79) |
| 2 | 1209 (14) | 143 (11) | 18 (8.5) | 1370 (14) |
| 3 | 334 (4.0) | 22 (1.5) | 5 (3.0) | 361 (4.0) |
| 4 | 51 (0.5) | 7 (0.5) | 1 (0.5) | 59 (0.5) |
| 5 or more | 16 (0.5) | 2 (0.5) | 2 (1.0) | 20 (0.5) |
| Missing | 204 (3.0) | 26 (1.5) | 16 (8.0) | 246 (2.0) |
| **Immediate mechanical complications** | | | | |
| Any | 453 (5.5) | 66 (5.0) | 27 (14) | 546 (5.5) |
| Failed insertion[e] | 177 (2.1) | 27 (2.0) | 12 (6.1) | 216 (2.2) |
| Bleeding[f] | 131 (1.6) | 13 (1.0) | 10 (5.1) | 154 (1.6) |
| Punctured artery | 87 (1.0) | 16 (1.2) | 5 (2.6) | 108 (1.1) |
| Arrhythmia | 47 (0.6) | 6 (0.5) | 0 (0.0) | 53 (0.5) |
| Pneumothorax | 11 (0.1) | 4 (0.3) | 0 (0.0) | 15 (0.1) |
| **Total catheter days** | 48899 | 12725 | 916 | 62540 |
| Days with catheter | 5 [2—9] | 6 [3—14] | 3 [1—7] | 5 [2—10] |
| Missing | 1779 (21) | 260 (20) | 31 (16) | 2070 (21) |

[a] Numbers are presented as number (%) and continuous variables are presented as median [interquartile range].
[b] Registering multiple indications for one insertion was possible. Example of indications labeled as "Other" were introducer, pacemaker, continuous renal replacement therapy or dialysis.
[c] Registering multiple anticoagulative treatments for one insertion was possible.
[d] Registering multiple thrombotic treatments for one insertion was possible.
[e] "Failed insertions" included insertions with change of blood vessel and insertion attempts where no CVC was inserted.
[f] Grade 1 bleedings were not registered in this study. In this study 99.4 % of all bleedings could be classified according to Common Terminology Criteria for Adverse Events (CTCAE; Version 5.0) as grade 2. One grade 4 bleeding occurred also included in the" Bleeding" category.

variables. Baseline variables were considered as potential independent variables and differences between cases with tip colonisation and CRI were tested against controls using univariate regression analyses. Given a presumed complex interdependence of the independent variables, we also performed a multivariable logistic regression for all outcomes. The number of independent variables in the multivariable logistic regression models was limited so that maximum one independent variable per ten events was included. The selection of independent variables in the multivariable regression model was based on results from previous studies and results from the univariate analyses [4,7,12,16]. The Hosmer-Lemeshow test was used to test goodness of fit for multivariable testing. $P<0.05$ was considered significant and all tests were two tailed.

## Results

In summary, a total of 9924 catheter insertions in 6872 patients were included in the study during the study period of 18 months (Figure 1). Data from the CVC insertion template, automatically extracted from the EHR, are presented as baseline characteristics of patients and CVCs in Table I. The most common insertion site was the jugular vein (85%) and the majority of catheters were inserted in an operating theatre (54%). Immediate complications after CVC insertion occurred in 5.5% of cases, where failed insertion (change of blood vessel or abandoned attempt of insertion) was most common (2.2%), followed by bleeding (1.6%) and punctured artery (1.1%).

In total, 2304 (23%) CVCs were sent for culture (Figure 1). A total of 257 (2.6%) of all 9924 catheters demonstrated a positive tip culture, yielding a colonisation incidence of 4.1 tip colonisations/1000 catheter days. Further, CRI was confirmed in 74 cases (0.7%) yielding a CRI incidence of 1.2/1000 catheter days. Simultaneous blood culture and tip cultures were obtained in 667 cases (6.7%) with suspected infection where these cultures yielded positive results in 69 cases (0.7%). However, only 20 cases met the criteria for CRBSI (0.2%), resulting in a CRBSI incidence of 0.3/1000 catheter days. Due to unknown catheter durations, a total of 2070 catheters (all without colonisation and positive tip culture) were excluded when calculating the incidences.

To evaluate any impact on the COVID-19 pandemic, a comparison between the prevalence of catheter colonisation/CRI/CRBSI during six months in the pandemic and the corresponding six months the year before, was performed. The analyses demonstrated no differences between the periods (Table II).

All isolated organisms are presented in Table III. The pathogens isolated in tip and blood cultures predominantly consisted of *Staphylococci*, where *Staphylococcus epidermidis* was by far the most common species. In fact, *S. epidermidis* was the only coagulase negative staphylococcus identified in CRI and CRBSI. In tip cultures *S. epidermidis* was seen in 64%

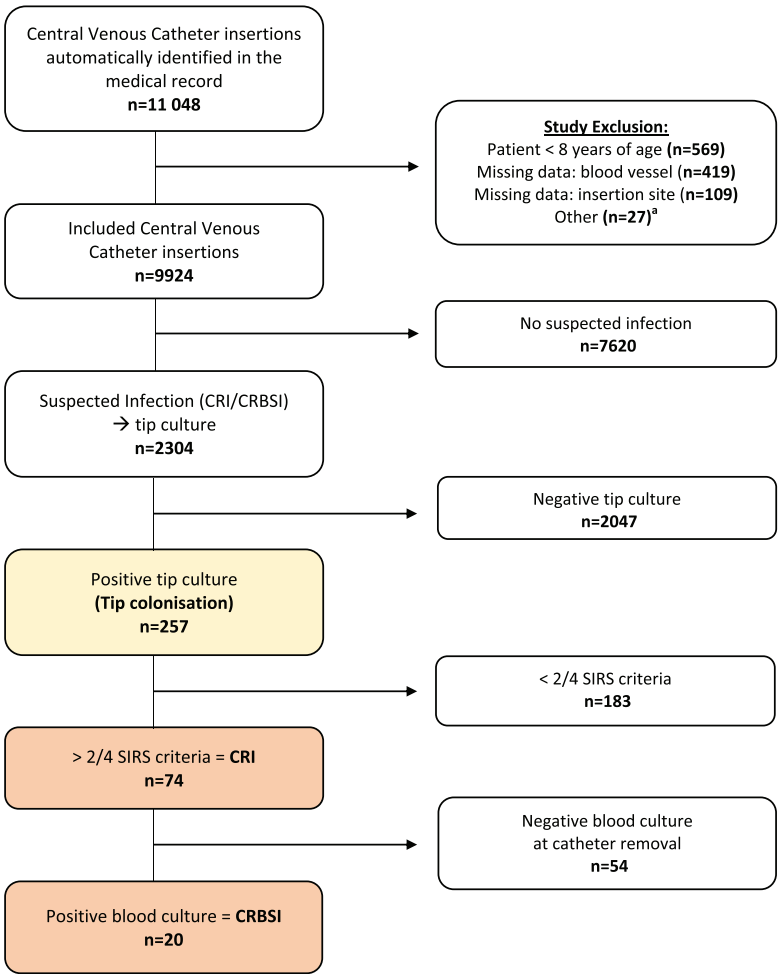


**Figure 1.** Flow chart with the number of Catheter Tip Colonisations, Catheter Related Infections (CRI) and, Catheter Related Bloodstream Infection (CRBSI) between March 2019 and August 2020 in Region Skåne, Sweden. Abbreviations: SIRS, systemic inflammation response syndrome.[a] Peripherally inserted catheters, or insertion missing both insertion site and insertion date.

and *S. aureus* in 12% of all tip cultures. The microorganisms responsible for CRI and CRBSI respectively was *S. epidermidis* (66% and 40%), *S. aureus* (15% and 35%), various Gram negatives (12% and 10%) and yeasts (12% and 10%)

The univariate regression analysis is described in detail in Table IV. The goodness of fit in the multivariable regression analyses showed a valid chi-square value ($P > 0.05$) for both models. The detailed results of the multivariable regression analyses are shown in Table V. In summary, 13 independent variables were selected for investigation of tip colonisation ($n=257$) and seven independent variables for CRI ($n=74$). Male gender and increased number of catheter lumens were

**Table II**
Impact of COVID-19 pandemic on colonisation, CRI and CRBSI

| Period | Colonisation (n=257) | CRI (n=74) | CRBSI (n=20) |
|---|---|---|---|
| March 2019–August 2019 | 94 | 27 | 7 |
| March 2020–August 2020 | 96 | 28 | 7 |
| | *P = 0.8538* | *P = 0.9652* | *P = 0.9283* |

The study was conducted between March 2019 and August 2020. During this time-period, the included hospitals received patients with COVID-19 between March 2020 and August 2020. Prevalences were compared between March 2019–August 2019 and March 2020 -August 2020. Using the Chi-square test, no significant difference in infection prevalence was seen between the COVID-19 free period and the first wave of the COVID-19 pandemic.

independently associated with both catheter tip colonisation and CRI. Increased number of days with catheter and CVCs inserted in patients admitted to a medical ward were associated with increased tip colonisation, while catheters inserted in the subclavian vein were associated with decreased catheter tip colonisation compared with insertions in the jugular vein. As the frequency of CRBSI (n=20) was low, no regression analyses were performed for CRBSI. The characteristics of cases with CRBSI are presented in Table VI.

## Discussion

This observational multicentre follow-up study on 9924 CVC insertions demonstrated low incidences of CRI and CRBSI. Several associations between independent variables and CRI were identified, where catheter tips were observed as less likely to be colonised when the subclavian route was used compared to the internal jugular route and where male sex as well as increased number of catheter lumens were both associated with catheter tip colonisation and CRI. Furthermore, the automatic script-based extraction from the EHR was feasible and may be the base for future continuous CRI surveillance.

We designed the present study in an attempt to a follow-up of the results previously published by us where 1722 central venous catheter insertions inserted between the years 2011 and 2012 at a University Hospital in the same Region as the present, was investigated [4]. The previous study demonstrated an incidence of CRI and CRBSI of 1.86 and 0.62, per 1000 catheter days after the implementation of simple hygiene insertion bundles. In the present study the same point estimates were 1.2 and 0.3/1000 catheter days. These results indicate that the low incidence of CRI and CRBSI remains. However, it should be noted that there was significant time between the study periods, the present study included significantly more cases (9924 vs. 1722), used an automated script-base data-extraction from the EHR (compared to manual review), also included cases from the whole Scania Region and not only from one hospital.

Furthermore, the present study indicates that pathogens previously associated with CRI and CRBSI (Table III), as presented by Thorarinsdottir *et al.* [4], still represent most cases

**Table III**
Isolated microorganisms from central venous catheter (CVC) tips[a]

| Organism | Colonised tips (n=257) | CRI (n=74) | CRBSI (n=20) |
|---|---|---|---|
| **Gram positives:** | 216 (84) | 66 (89) | 16 (80) |
| *Staphylococcus* | 164 (64) | 49 (66) | 8 (40) |
| Coagulase negative (total)[b] | | | |
| *S. epidermidis* | *152 (59)* | *49 (66)* | *8 (40)* |
| *S. warneri* | *1 (0.4)* | *0 (0.0)* | *0 (0.0)* |
| *S. capitis* | *5 (1.9)* | *0 (0.0)* | *0 (0.0)* |
| *S. caprae* | *2 (0.8)* | *0 (0.0)* | *0 (0.0)* |
| *S. hominis* | *1 (0.4)* | *0 (0.0)* | *0 (0.0)* |
| *S. haemolyticus* | *1 (0.4)* | *0 (0.0)* | *0 (0.0)* |
| *S. simulans* | *1 (0.4)* | *0 (0.0)* | *0 (0.0)* |
| *S. lugdunensis* | *1 (0.4)* | *0 (0.0)* | *0 (0.0)* |
| *Staphylococcus aureus* | *32 (12)* | *11 (15)* | 7 (35) |
| other | *8 (3.0)* | *1 (1.0)* | 0 (0.0) |
| *Enterococcus* | | | |
| *faecalis* | *3 (1.0)* | *1 (1.0)* | 0 (0.0) |
| *faecium* | *4 (2.0)* | *3 (4.0)* | 1 (5.0) |
| Other | *5 (2)* | *1 (1)* | 0 |
| **Gram negatives:** | **22 (9.0)** | **9 (12)** | **2 (10)** |
| *Pseudomonas aeruginosa* | *5 (2.0)* | *3 (4.0)* | 1 (5.0) |
| *Klebsiella* | | | |
| *pneumoniae* | 4 (2.0) | 1 (1.0) | 0 (0.0) |
| *aerogenes* | 2 (0.8) | 2 (3.0) | 0 (0.0) |
| *Serratia marcescens* | 4 (2.0) | 1 (1.0) | 1 (5.0) |
| *Escherichia coli* | 3 (1.0) | 1 (1.0) | 0 (0.0) |
| Other | 4 (2.0) | 1 (1.0) | 0 (0.0) |
| **Yeasts:** | **19 (7.0)** | **9 (12)** | **2 (10)** |
| *Candida* | | | |
| *albicans* | 8 (3.0) | 6 (8.0) | 1 (5.0) |
| *glabrata* | 3 (1.0) | 2 (3.0) | 1 (5.0) |
| *parapsilosis* | 3 (1.0) | 1 (1.0) | 0 (0.0) |
| other | 5 (2.0) | 0 (0.0) | 0 (0.0) |

[a] Numbers are presented as number (%). Registering multiple pathogens for one CVC tip was possible.
[b] Coagulase negative staphylococci were type speciated using the MALDI-TOF technique.

of CVC infections at the studied hospitals. *S. epidermidis* has previously been described as the most common coagulase negative staphylococcus species in CRI [17]. In the present study, *S. epidermidis* was the only coagulase negative staphylococcus responsible for CRI and CRBSI. When comparing these results with previous national studies on CRI [7,18], we observe regional differences in pathogen growth. Hence, these findings could impact local infection management strategies to prevent certain pathogens from causing CRI. As an example, antifungal treatment could be considered when treating suspected CVC infections in regions with higher incidences of CRI caused by *Candida* spp.

In the logistic regression analysis (Table V), we identified associations between independent variables and catheter tip colonisation as well as CRI. First, longer catheterisation times

**Table IV**
Univariate analysis of potential risk factors for central venous catheter (CVC) tip colonisation and catheter-related infection (CRI). Data from between March 2019 and August 2020 in Region Skåne, Sweden[a]

| Independent variables | Tip colonisation | | | CRI | | |
|---|---|---|---|---|---|---|
| | Tip colonisation (n=257) | 95% CI | P-value | CRI (n=74) | 95% CI | P-value |
| Age | 66 [56–75] | 0.99–1.01 | 0.832 | 65 [57–75] | 0.98–1.01 | 0.786 |
| Sex, male | 173 (67) | 1.03–1.74 | 0.032 | 54 (73) | 1.04–2.92 | 0.034 |
| Days with catheter | 8 [2–14] | 1.01–1.02 | 0.002 | 6 [1–11] | 0.98–1.02 | 0.985 |
| Central Haemodialysis Catheter vs Central Venous Catheter | 23 (9.0) | 1.43–3.44 | <0.001 | 8 (11) | 1.28–5.62 | 0.009 |
| Catheter lumens | - | 1.41–1.72 | <0.001 | 4 [3–5] | 1.58–2.31 | <0.001 |
| **Insertion site** | | | | | | |
| Jugular vein (reference) | 236 (92) | - | - | - | - | - |
| Subclavian vein | 17 (6.5) | 0.27–0.74 | 0.001 | 5 (7.0) | 0.18–1.13 | 0.090 |
| Femoral vein | 4 (1.5) | 0.26–1.96 | 0.520 | 0 (0.0) | - | 0.995 |
| **Anticoagulant treatment before insertion**[b] | 197 (77) | 1b05–1.89 | 0.023 | 59 (80) | 0.66–2.06 | 0.601 |
| **Procoagulant treatment before insertion** | 218 (85) | 0.82–1.64 | 0.398 | 63 (85) | 0.59–2.15 | 0.711 |
| **Room intended for CVC insertion** | | | | | | |
| Operating theatre (reference) | 96 (38) | - | - | - | - | - |
| Intensive Care Unit | 112 (44) | 1.86–3.24 | <0.001 | 37 (50) | 1.91–5.35 | <0.001 |
| Room reserved for CVC-insertion | 34 (13) | 0.98–2.15 | 0.066 | 6 (8.0) | 0.41–2.48 | 0.975 |
| Patient ward | 12 (5.0) | 1.30–4.41 | 0.005 | 5 (7.0) | 1.49–10.38 | 0.006 |
| **Department of admission at CVC insertion** | | | | | | |
| Surgical ward (reference) | 83 (34) | - | - | - | - | - |
| Medical ward | 82 (33) | 1.27–2.36 | <0.001 | 20 (27) | 0.83–2.76 | 0.178 |
| Intensive Care Unit | 81 (33) | 2.30–4.29 | <0.001 | 27 (36) | 2.11–6.46 | <0.001 |
| **High risk patient**[c] | 90 (35) | 1.50–2.53 | <0.001 | 29 (39) | 1.44–3.70 | <0.001 |
| **Number of skin punctures** | | 0.68–1.03 | 0.099 | - | 0.58–1.26 | 0.431 |
| **Number of punctured blood vessels** | | 0.71–1.15 | 0.419 | - | 0.65–1.49 | 0.921 |
| **Immediate mechanical complications** | | | | | | |
| No (reference) | 243 (95) | - | - | - | - | - |
| Bleeding/punctured artery | 6 (2.0) | 0.66–2.75 | 0.422 | 2 (3.0) | 0.28–4.74 | 0.841 |
| Other | 8 (3.0) | 0.43–2.23 | 0.962 | 2 (3.0) | 0.28–4.66 | 0.860 |

[a] Numbers are presented as number (%) and continuous variables are presented as median [interquartile range].
[b] Warfarin and Non-vitamin K Antagonist Oral Anticoagulants were categorized as anticoagulative treatment, while Low Molecular Weight Heparin and Acetylsalicylic Acid were not.
[c] Immunocompromised patients.

were associated with catheter tip colonisation, but not with CRI. Previous studies have convincingly demonstrated that the time with the catheter correlates positively with the risk of CRI and CRBSI [7,18]. As noted by Hammarskjöld *et al.*, adequate adherence to routines advocating early removal of unnecessary catheters could minimize the effect of correlations between catheterisation time and CRI [7]. It has been suggested that catheter tip colonisation is a predisposal factor for CRI and CRBSI, hence we suggest that common practice should continue to prioritise the immediate removal of unnecessary CVCs [19]. Moreover, the current study demonstrates that CVCs inserted in the subclavian vein were associated with less catheter tip colonisation compared to insertion in the jugular vein. The insertion site, however, was not confirmed to affect the risk of CRI in this study.

Secondly, our results show that male sex and increased number of catheter lumens were associated with both catheter tip colonisation and CRI. Increased risk of catheter tip colonisation in men has previously been demonstrated in a retrospective study from 2008 by Gowardman *et al.* [16]. Studies linking gender to risk of CRI, however, are scarce. In a prospective study by Moro *et al.*, it was shown that men present an increased risk for skin colonisation at the CVC insertion site, which showed an increased risk of CRI, especially when using the jugular vein as point of insertion [20]. Furthermore, beard growth and shaving may not only facilitate pathogen multiplication, but has also been observed to reduce adherence of wound dressing materials, suggesting increased risk of bacterial contamination [21]. Increased number of CVC lumens being an associated risk factor for CRI has previously been reported [4,22], thus advocating for minimising the number of catheter lumens when choosing a CVC.

Thirdly, our results also indicate that CVCs inserted in patients admitted to a medical ward present an increased likelihood of catheter colonisation, when compared with patients admitted to a surgical ward. Several studies have evaluated the rates of CRI among inpatients receiving CVCs,

**Table V**
Multivariable logistic regression analyses for tip colonisation and catheter-related infection (CRI)[a]

| Independent variables | Tip colonisation | | | CRI | | |
|---|---|---|---|---|---|---|
| | Odds Ratio | 95% CI | P-value | Odds Ratio | 95% CI | P-value |
| Age | 1.01 | 0.99–1.01 | 0.676 | 1.01 | 0.98–1.02 | 0.876 |
| Sex, male | 1.50 | 1.11–2.04 | 0.008 | 2.06 | 1.13–3.78 | 0.019 |
| Days with catheter | 1.02 | 1.01–1.03 | <0.001 | 1.02 | 0.99–1.04 | 0.130 |
| Catheter lumens | 1.57 | 1.37–1.80 | <0.001 | 1.95 | 1.54–2.47 | <0.001 |
| **Insertion site** | | | | | | |
| Jugular vein (reference) | - | - | - | - | - | - |
| Subclavian vein | 0.36 | 0.21–0.63 | <0.001 | 0.37 | 0.13–1.04 | 0.059 |
| Femoral vein | 0.42 | 0.10–1.73 | 0.070 | - | - | 0.996 |
| **Room intended for CVC insertion** | | | | | | |
| Operating theatre | 0.68 | 0.45–1.03 | 0.071 | 0.62 | 0.30–1.27 | 0.190 |
| **High risk patient**[b] | 0.83 | 0.54–1.28 | 0.397 | 0.71 | 0.33–1.51 | 0.371 |
| **Department of admission at CVC insertion** | | | | | | |
| Surgical ward (reference) | - | - | - | | | |
| Medical ward | 1.49 | 1.02–2.18 | 0.037 | | | |
| Intensive Care Unit | 1.18 | 0.72–1.95 | 0.511 | | | |
| **Anticoagulant treatment before insertion**[c] | 1.35 | 0.98–1.88 | 0.070 | | | |
| **Immediate mechanical complications** | | | | | | |
| No (reference) | - | - | - | | | |
| Bleeding/punctured artery | 0.67 | 0.21–2.16 | 0.507 | | | |
| Other | 1.00 | 0.43–2.31 | 0.999 | | | |

[a] Abbreviations: catheter related infections (CRI), central venous catheter (CVC).
[b] Immunocompromised patients.
[c] Warfarin and NOACs were categorized as anticoagulative treatment, while Low Molecular Weight Heparin and Acetylsalicylic Acid were not.

with varying results [23]. As summarised by Kallen *et al.*, the differences in infection rates in different units can vary depending on the type of unit and teaching status of the facility [23]. In the light of this, it is more likely that the cause of the association between CVCs inserted in patients admitted to a medical ward and catheter tip colonisation is driven by a risk of bias in the selection of patients, where patients admitted to medical wards tend to be more immunocompromised and therefore more susceptible to infection.

By comparing this current study with previously conducted studies from the same region [4,24], it was used as a follow-up study on local CVC management. The results showed a sustained low CRI incidence. Hence, the study served as a quality improvement report indicating continuous safe CVC-routines in the studied region. Nevertheless, a low incidence is still not equal to zero and complete eradication of CRI should be the goal of any future interventions. As previously shown by Longmate *et al.* [5], rigorous hygiene and educational interventions can lead to complete elimination of CRI. Hence, a vision zero for CRI should be adopted as an ethical stance as it has been demonstrated possible to eradicate completely [25]. However, as part of an eradication process, CRI incidence should be evaluated longitudinally. Therefore, we need to find an efficient and systematic way to assess CRI over time.

In our study, as well as in more recent epidemiological studies on CRI and sepsis, but also generally, search queries and automatic script-based data extraction seems to be an efficient way of tracking medical device management and infection incidences [8–11,26]. As an example, Gokhale *et al.* recently presented a tool used for automatic data extraction for epidemiological research, using a process that can be verified and reproducible [26]. The study highlights how this new process of extracting available information reduces the gap between medical researchers and electronic records, enabling continuous quality surveillance.

Given that EHR (electronic health records) are increasingly used in healthcare systems for documentation, the potential power of the fully automated surveillance systems is yet to be discovered and evaluated. Data from EHRs has the potential to replace time consuming and subjective manual chart review-surveillance and may also provide continuous surveillance, such as in this study, which is the first one to our knowledge applying it to follow-up previous results. The automated electronic surveillance systems must be carefully evaluated, and the construction of the systems is resource consuming but once implemented, these systems have the potential to provide invaluable real-time quality assurance, superior to current standard. However, further research in this area, where we examine data abstraction methods across hospitals and validate automated data extraction systems, are still needed [27].

We recognise the limitations in the present study given the retrospective design. Although there is a strong tradition in the studied departments to document every CVC-insertion, it cannot be ruled out that single insertions were not documented. Although, we have tried to correct for confounders in the multivariable logistic regression analyses and the goodness of fit test was good, the presence of occult independent

**Table VI**
Characteristics of patients with confirmed catheter related bloodstream infection (CRBSI)[a]

| Variable | No CRBSI (n=9904) | CRBSI (n=20) |
|---|---|---|
| Age | 69 [57–76] | 66 [53–71] |
| Sex, male | 6027 (61) | 11 (55) |
| Days with catheter | 5 [2–10] | 6 [1–15] |
| Central Haemodialysis Catheter vs Central Venous Catheter | 430 (4.0) | 4 (20) |
| **Catheter lumens** | | |
| 1 | 2645 (27) | 2 (10) |
| 2 | 2186 (22) | 3 (15) |
| 3 | 2793 (28) | 2 (10) |
| 4 | 666 (7.0) | 0 (0.0) |
| 5 | 994 (10) | 9 (45) |
| **Insertion site** | | |
| Jugular vein | 8381 (85) | 17 (85) |
| Subclavian vein | 1327 (13) | 3 (15) |
| Femoral vein | 196 (2.0) | 0 (0.0) |
| **Anticoagulant treatment at insertion** | 8127 (82) | 16 (80) |
| **Procoagulant treatment before insertion** | 8577 (87) | 17 (85) |
| **Room intended for CVC insertion** | | |
| Operating theatre | 5336 (54) | 3 (15) |
| Intensive Care Unit | 2604 (26) | 12 (60) |
| Room reserved for CVC insertion | 1321 (13) | 2 (10) |
| Patient ward | 286 (3.0) | 2 (10) |
| **Department of admission at CVC insertion** | | |
| Surgical ward | 5042 (51) | 3 (15) |
| Medical ward | 2905 (29) | 5 (25) |
| Intensive Care Unit | 1615 (16) | 9 (45) |
| **High risk patients** | 2159 (22) | 10 (50) |
| **Number of skin punctures** | | |
| 1 | 7450 (75) | 18 (90) |
| 2 | 1545 (16) | 1 (5.0) |
| 3 | 516 (5.0) | 0 (0.0) |
| 4 | 122 (1.0) | 0 (0.0) |
| 5 or more | 60 (1.0) | 0 (0.0) |
| **Number of punctured blood vessels** | | |
| 1 | 7850 (79) | 18 (90) |
| 2 | 1369 (14) | 1 (5.0) |
| 3 | 361 (4.0) | 0 (0.0) |
| 4 | 59 (1.0) | 0 (0.0) |
| 5 | 20 (0.2) | 0 (0.0) |
| **Immediate mechanical complications** | | |
| No | 9432 (95) | 20 (100) |
| Bleeding/punctured artery | 238 (2.0) | 0 (0.0) |
| Other | 234 (2.0) | 0 (0.0) |

[a] Numbers are presented with number (%) and continuous variables are presented with median [interquartile range]. Missing data is not presented in table.

variables affecting the outcome still cannot be ruled out. Further, the sample size was based on the number of available insertions during the study period meaning that the power of the results is uncertain. Last, the sensitivity of the automated script-base data extraction from the EHR has not been investigated in the current study.

In summary, this large retrospective observational study demonstrated that automated data extraction of EHR data could be the base for quality assurance and epidemiological studies. Furthermore, the results indicate a sustained low incidence of CRI and CRBSI in the region and several associations between independent variables and both catheter tip colonisation and CRI, were identified. In addition, this study demonstrates that the choice of insertion site might impact the catheter tip colonisation rate. Male sex and an increased number of catheter lumens were associated with both catheter tip colonisation and CRI.

## Credit author statement

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**Mika M. Rockholt:** Conceptualization, Methodology, Formal Analysis, Writing — Original Draft, Writing — Review & Editing, Visualization.

**Tobis Agrell:** Formal Analysis, Writing — Original Draft, Writing — Review & Editing.

**Hulda Thorarinnsdottir:** Writing — Review & Editing, Supervision.

**Thomas Kander:** Conceptualization, Methodology, Formal Analysis, Writing — Review & Editing, Supervision, Project Administration.

## Conflict of interest

Thomas Kander is on the Advisory Board of Bactiguard AB (Stockholm, Sweden) and of Anaesthesiology Intensive Therapy (Poland). The remaining authors have no conflicts of interest to declare.

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