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Multimodal and multidisciplinary strategies in the prevention of healthcare-associated infections – the example of catheter-associated bloodstream infections

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**UNIVERSITÉ
DE GENÈVE**



Hôpitaux
Universitaires
Genève

University of Geneva Hospitals
Infection Control Programme

**MULTIMODAL AND MULTIDISCIPLINARY STRATEGIES IN
THE PREVENTION OF HEALTHCARE-ASSOCIATED
INFECTIONS – THE EXAMPLE OF CATHETER-
ASSOCIATED BLOODSTREAM INFECTIONS**

Thesis submitted to the Medical School of the University of Geneva

for the degree of Privat-Docent

by

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Geneva

2015

Direction Médicale

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Université de Genève

Hôpitaux Universitaires de Genève

MULTIMODAL AND MULTIDISCIPLINARY STRATEGIES IN THE PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS – THE EXAMPLE OF CATHETER- ASSOCIATED BLOODSTREAM INFECTIONS

**Thèse d'habilitation présentée à la Faculté de Médecine de
l'Université de Genève pour l'obtention du titre de
Privat-Docent par le Dr méd Walter Zingg**

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Thèse de Privat-Docent

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SUMMARY

Healthcare-associated infections (HAIs) affect hundreds of millions of patients worldwide each year. In the European Union alone, the annual number of HAIs can be estimated at 4,544,100 with approximately 37,000 deaths as a direct consequence. Bloodstream infections represent about 12% of all HAI with higher proportions among children (27%) and neonates (59%). Most healthcare-associated bloodstream infections are catheter-associated (CABSI). HAI are largely preventable and reducing CABSI has become the paradigm of successful infection prevention and control (IPC) interventions. While prevention activities focused on the use of technology in the past, a growing number of studies showed that behaviour change interventions are far more effective in CABSI reduction. This was evidenced in a recent large systematic review about successful organisation and structure in IPC, which was performed at the University of Geneva Hospitals (HUG) in collaboration with the European Centre for Disease Prevention and Control. Behavioural change interventions are complex and such programmes must follow a multimodal strategy developed by multidisciplinary teams, and taking into account local conditions. Multimodal strategies are a combination of technology and best practice, which are delivered by different “modes” such as lectures, visual reminders, simulation training, bedside teaching, knowledge tests, or any other original and imaginable idea to change the behaviour of healthcare professionals. Preparation and implementation must include stakeholders from different disciplines and professions and education and training must involve frontline staff. Two projects which were coordinated by the applicant at the University Hospital of Zurich and at HUG are examples of successful multimodal prevention strategies. The projects promoted comprehensive best practice procedures and both used different modes and professions to provide education and training. The major challenge for HAI prevention is “implementation” and more research must be invested on this aspect in the future in order to provide hospitals with manageable information about how to conduct effective multimodal strategies in daily practice.

REVIEW

Healthcare-associated infections (HAIs) affect hundreds of millions of patients worldwide each year.^{1,2} In the European Union alone, the annual number of HAIs can be estimated at 4,544,100 with approximately 37,000 deaths as a direct consequence, and 16 million extra-days of hospital stay as estimated by the European Centre for Disease Prevention and Control (ECDC).⁴ Based on a multi-state point prevalence survey, the most recent assessment of the annual number of patients with HAI in the USA was estimated at 648,000 in acute care hospitals.⁵ In Switzerland, the annual number of HAI has been estimated at approximately 70,000 (personal communication, *Swissnoso*).

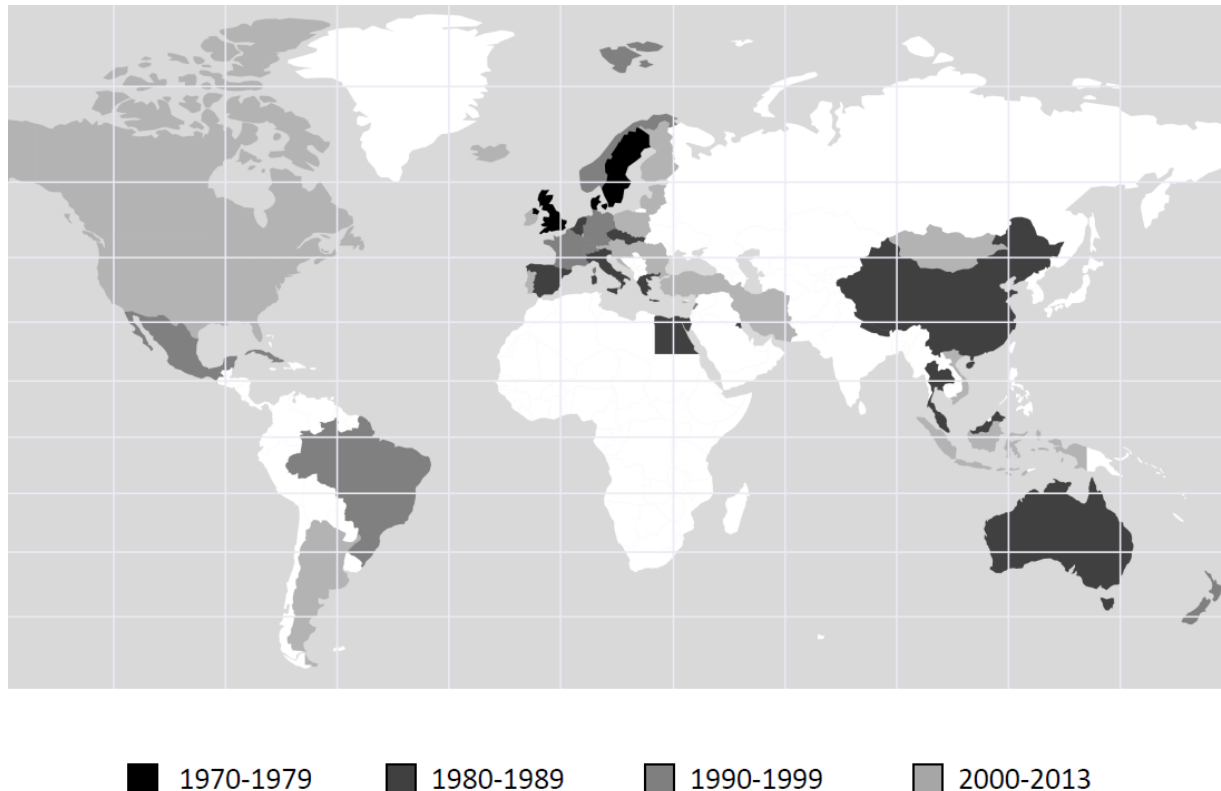
Epidemiology of healthcare-associated infections

The United States (US) National Nosocomial Infection Surveillance (NNIS) network started to measure prospective outcome data on HAI in intensive care units (ICUs) in the USA in 1970.^{6,7} This system was transferred to the National Healthcare Safety Network (NHSN) in 2005.⁸ Based on this work and the US Centers for Disease Control and Prevention (CDC) definitions,⁹ a number of national and international surveillance networks were established, such as the European initiative Hospitals in Europe Link for Infection Control through Surveillance (HELICS) in 1994, the German Krankenhaus Infektions Surveillance System (KISS) programme in 1996,¹¹ and the International Nosocomial Infection Control Consortium (INICC) in 2002.¹² Although participation in these surveillance programmes is voluntary, peer pressure among hospitals or from public reporting programmes can act as a lever and “encourage” them to enrol in such networks,¹³ and participation in some of the networks has become mandatory as part of a national patient safety strategy. Since 2006, all neonatology units in Germany must participate in the German Neo-KISS programme for very-low-birth-weight (VLBW) infants (<1500g).^{14,15} Outcome surveillance of the US NHSN with reporting to the CDC has become mandatory in 32 states of the USA as of March 2015.¹⁶ In 2010, 16 of 33 European countries had a scheme in place for the reporting of HAI data to national healthcare authorities.¹⁷ In addition, 7 countries (France, Ireland, Norway, and four UK

Historically, HAI incidence data have been measured in risk areas, e.g., intensive care units (ICUs),²⁵⁻²⁹ oncology units,^{30,31} or burn units,³² or they addressed selected (indicator) surgical procedures.²⁷ Selected HAI surveillance targets include primary or central line-associated BSI (CLABSI), catheter-related BSI (CRBSI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), (catheter-associated) urinary tract infections (CAUTI), and SSI for selected procedures.³³ Only recently has surveillance also included regular acute care units.^{26,34,35}

Prospective HAI surveillance is resource intensive and as a consequence information on hospital-wide HAI incidence is sparse. Hospital-wide data more often come from point or period prevalence surveys.⁷ In 1981, the World Health Organization (WHO) convened an advisory group on the surveillance, control, and prevention of HAI.³⁶ The group specifically recommended the conduct of HAI prevalence surveys to assess the burden of the problem in different parts of the world. Later, WHO published prevalence data gathered between 1983 and 1985 from 47 hospitals in 14 countries.³⁶ At the same time, an increasing number of countries started to conduct national or regional prevalence surveys as was summarized by Zingg and colleagues in a recent report (Figure 2).⁷

Figure 2: First international, national, or regional prevalence surveys of healthcare-associated infections in acute or mixed care settings: 1970–2013.⁷



(Produced with “worldmapgenerator.com”; published in Zingg et al.⁷)

Most local, regional, and national surveys used the point prevalence methodology, i.e., only HAIs active on the day of survey are taken into account.⁷ However, some studies in Italy,^{37,38} Switzerland,³⁹⁻⁴² and the USA⁴³ used the period prevalence method, i.e., not only HAIs active on the day of the survey, but also an assessment of those active during a pre-defined period before the survey day. Some surveys, such as the first Spanish prevalence survey of the EPINE network (Estudio de Prevalencia de las Infecciones Nosocomiales en España) combined point prevalence with extrinsic risk factors present in the 7 days before the survey.⁴⁴ Both methodologies have advantages and disadvantages. While a period prevalence will allow to capture more HAIs, especially those of short duration, it is methodologically a mix between the concepts of “prevalence” and “incidence” and is also more time- consuming than a point prevalence.⁷ Primary BSIs are of longer duration and occur predominantly in acute care settings. A recent analysis to compare the point and

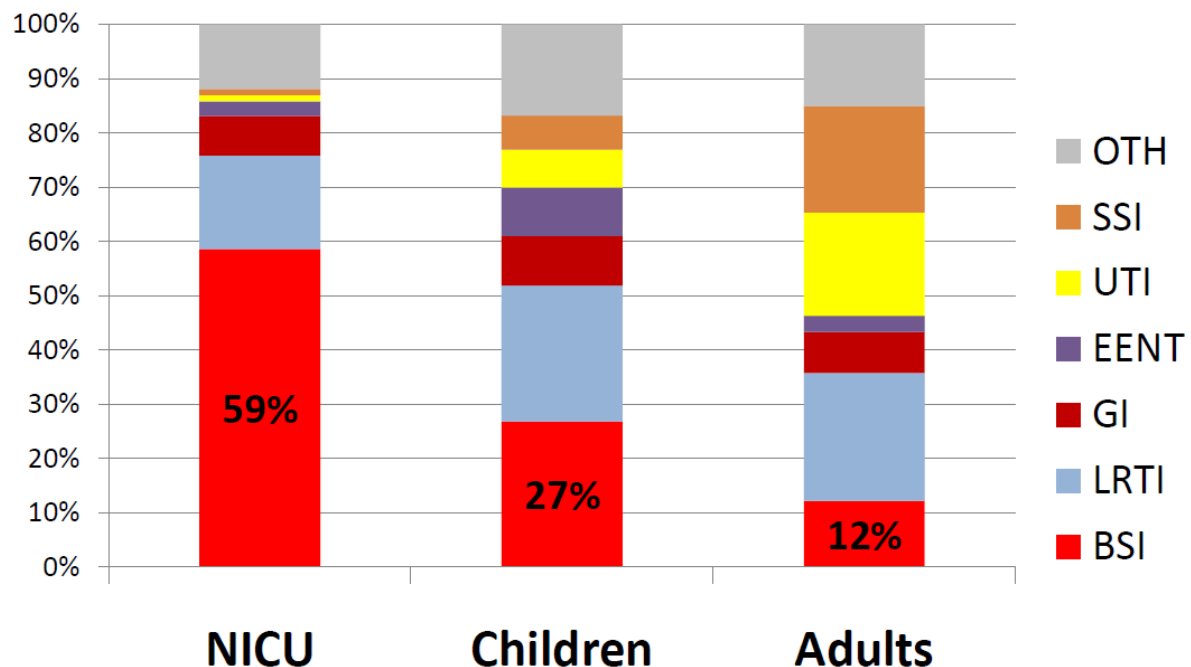
period methodologies by Zingg and colleagues used data from 7 annual prevalence surveys (2006-2012) with 10,367 patients at the University of Geneva Hospitals (HUG). The study did not find a significant difference (0.76% vs 0.86% [+13%]) between the two methods. The yearly prevalence surveys did not reflect decreasing BSI at HUG due to the positive effects of a CRBSI prevention programme (see below) that took place between 2008 and 2012, in contrast to prospective all-cause surveillance of laboratory-confirmed BSI.⁴⁵ Thus, prevalence surveys either using the point or the period methodology are not suited to detect prospective change of HAIs, even in a large institution such as HUG.^{7,46}

Most recently, the ECDC and the US CDC performed large point prevalence surveys based on the methodology published in two pilot studies.^{47,48} The point prevalence in the USA was 4.0% (95% CI: 3.7-4.4)⁵ with pneumonia (21.8%; [95% CI: 18.4–25.6]) and SSI (21.8% [18.4–25.6]) being the most commonly identified HAIs, followed by gastrointestinal infections (17.1% [14.0–20.5]), UTI (12.9% [10.2–16.0]), and primary BSI (9.9% [7.5–12.8]). The point prevalence in the European Union (EU) was 6.0% (country range: 2.3%–10.8%).⁴ The most frequently reported HAIs were respiratory tract infections (pneumonia 19.4%; lower respiratory tract 4.1%); SSI (19.6%); UTI (19.0%); BSI (10.7%); and gastrointestinal infections (7.7%), with CDI accounting for 48% of the latter.⁴

Epidemiology of healthcare-associated bloodstream infections

BSI represented 12% of all nosocomial infections reported in 10,038 patients from 1417 ICUs in the first European Prevalence of Infection in Intensive Care (EPIC) study.^{49,50} An even higher proportion (15%) among all HAIs was reported later worldwide in the Extended Prevalence of Infection in Intensive Care (EPIC2) study.^{50,51} Almost half of all positive blood cultures obtained in a hospital are due to HABSI, mostly associated with central lines.⁵⁰ The proportion of hospital-wide HABSI among HAI in acute care in the EU was 12.2%.⁴ This proportion was much higher (37.4%) among children in the ECDC point prevalence survey as reported by Zingg and colleagues (Figure 3).⁵²

Figure 3: Distribution of healthcare-associated infections among adults, children and neonates – ECDC point prevalence survey.⁵²



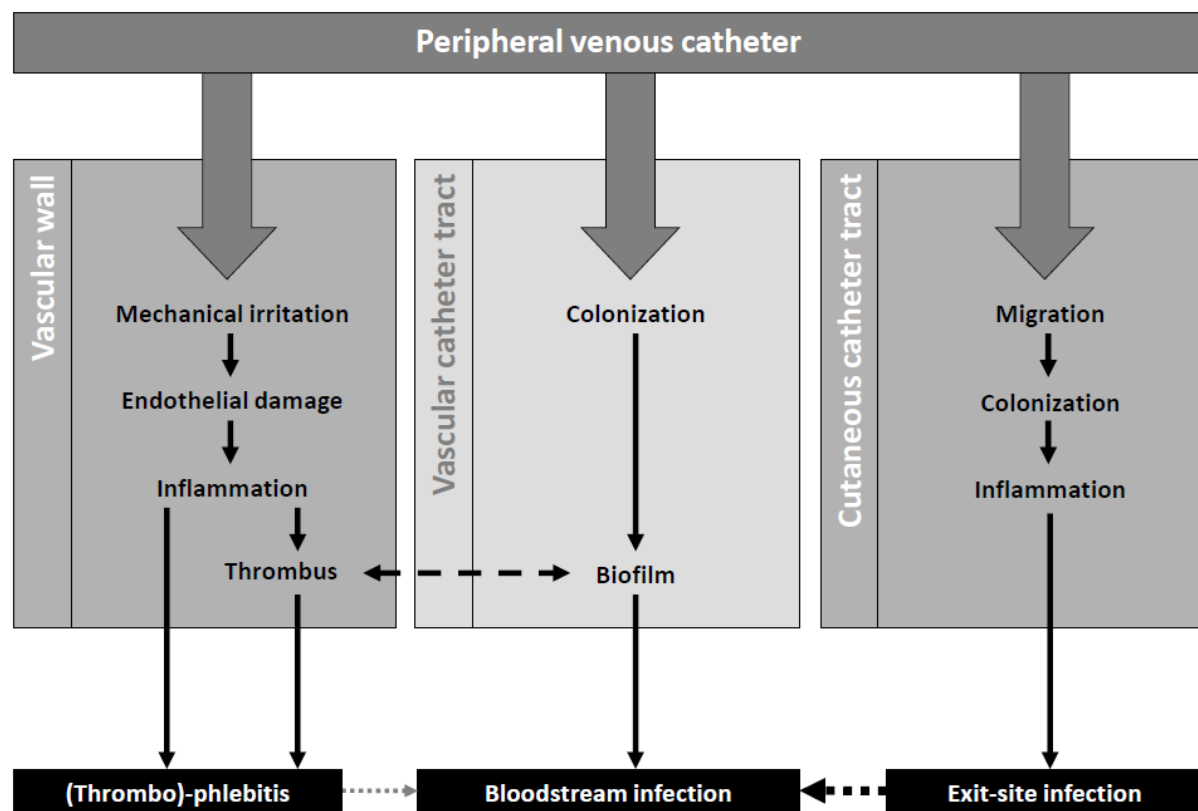
BSI: Bloodstream infection; EENT; Eye-ear-nose-throat infection; GI: Gastrointestinal infection; LRTI: Lower respiratory tract infection; OTH: other infection; SSI: Surgical site infection; UTI: Urinary tract infection

(Manuscript by Zingg et al. at ECDC for approval before submission)

The proportion of CLABSI/CRBSI varies among catheter types.⁵³ For peripheral venous lines, it represents approximately one-tenth of central venous catheters (CVCs) (0.2–0.5% versus 3–10%);⁵⁴⁻⁵⁶ by contrast, the proportion among arterial lines is low.^{56,57} The proportion of CRBSI in long-term tunnelled catheters is high (29%). However, the incidence density (CRBSI episodes per 1000 catheter days) is low (1.1/1000 catheter days).^{53,56,58} The rate of implantable port systems is even lower (5.7%; 0.1/1,000 catheter-days).^{53,56,59} The CRBSI risk for non-cuffed CVCs is high (5.0/1000 catheter-days) compared to other intravascular devices.^{53,56,60,61} Peripheral venous catheters (PVC) are the most frequently used invasive devices in hospitals. Up to 70% of patients receive a peripheral venous line during their

hospital stay, and conservative estimates suggest that PVC-days account for 15–20% of total patient-days in acute care.⁶² Only a few studies address the problem of PVC-associated BSI, mostly because the incidence density of PVC is low (0.05/1000 patient-days [95% CI: 0.03–0.6]),⁶³ and thrombophlebitis is a more common problem (Figure 4).⁶²

Figure 4: Overview of mechanisms for emerging thrombophlebitis, peripheral venous catheter-associated bloodstream infection and catheter exit-site infection.⁶²



(Published in Zingg et al.⁶²)

Central venous catheters

The first documented central venous line was a catheter to the right ventricle by Forssmann in 1929.⁵³ In 1952, Aubaniac reported using the subclavian vein as an access site,⁶⁴ 14 years before the access to the internal jugular vein was pioneered by Hermosura in 1966.⁵³

Mechanical complications, such as fractures and leakage of the catheter, air embolisms or hub separation were the predominant concerns in those days. However, catheter

colonization and CRBSI were soon described and recognized as relevant complications.⁶⁵

New catheter designs, such as the luer-lock mechanism or catheter cuffs, were developed to address such complications⁶⁶ and catheter materials like silicone and polyurethane were found to be less thrombogenic and less likely to colonize with pathogens.^{67,68}

Definitions of catheter-associated or catheter-related bloodstream infections

Definitions for nosocomial infections were issued by the CDC already in 1970,⁹ which allowed the US NNIS to start measuring prospective HAIs in ICUs in the same year.^{6,7} Over the following decades, the CDC HAI definitions were continually updated and became the reference standard for most HAI surveillance activities worldwide.^{7,9,12,69-73,75-78}

HAIs are defined as local or systemic infections with no evidence that the infection was present or incubating at the time of admission to the medical setting.⁷⁷ An arbitrary time period of 48 hours after admission is considered sufficient to distinguish between community- and hospital-acquired infections.⁷² The most recent CDC guidelines simplified the 48-hour rule by considering a healthcare association if all elements of a CDC/NHSN site-specific infection criterion are present together on or after day 3 of hospital stay (when admission day is day 1).⁸⁰

Three major groups of nosocomial CVC infections can be distinguished: 1) CVC exit-site infection; 2) CVC-associated clinical sepsis; and 3) primary laboratory-confirmed BSI either associated or related to a CVC.⁸⁰ Local inflammation at the CVC exit site including erythema, tenderness, warmth and/or purulent discharge is suggestive of an exit-site infection. If the catheter is removed and highly colonized with microorganisms, the local CVC infection may be associated with a potential systemic CRBSI and antibiotic therapy must be considered unless skin contaminants such as *S. epidermidis* or other coagulase-negative staphylococci (CoNS) are isolated. CVC-associated clinical sepsis is defined as fever, hypotension or oliguria in the presence of a CVC and without evidence of other infection sites, but without a

positive blood culture test (either not done or with a negative result). Although of benefit to the individual patient, clinical sepsis is not used for prospective CVC infection surveillance any longer, with the exception of neonates and infants in the first year of life.^{81,82} Primary laboratory-confirmed BSI is defined as bacteraemia identified by positive blood culture results. If skin contaminants are isolated, two positive blood culture tests drawn at different time points are required for the diagnosis. CLABSI or CRBSI is diagnosed by combining clinical signs, such as fever or systemic inflammatory response syndrome, with microbiological cultures. If a central line is in place at the time of laboratory-confirmed BSI but formal proof is lacking, CLABSI is diagnosed. Detection of identical species with the same susceptibility testing on the catheter tip confirms the catheter as a source (CRBSI). Alternatively, blood can be obtained from the catheter and from a peripheral vein. If the growth time of the blood sampling from the catheter is shorter than the growth time of the blood sampling from the peripheral vein by two hours or more, the catheter is the most likely source.⁸³ This test is called “differential time to positivity” and has the advantage that the catheter can be left in place.

Surveillance definitions and individual clinical definitions for CRBSI should be distinguished.⁸¹ The NHSN definition for laboratory-confirmed BSI is a reasonable surveillance definition, but somewhat overestimates the true CRBSI incidence density since bacteraemia may originate from sources difficult to document, such as abdominal translocation.⁵³ This is why the most recent NHSN guidelines introduced the new definition “Mucosal barrier injury laboratory-confirmed bloodstream infection” (MBI-LCBI).⁸⁰

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Skin contaminants are a challenge in CRBSI diagnosis because true infection can often neither be confirmed nor ruled out when such pathogens are isolated from a single blood culture and the patient is treated with antibiotics.⁵³ Considerable genotypical discordance was shown among CoNS when isolated from a peripheral vein and the catheter tip at the same time, thus raising the question whether CoNS should always be considered as contaminants or CoNS CRBSIs are more likely to be polyclonal, and thus, real.^{84,85} The NHSN guidelines require the same common commensal (i.e., diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., CoNS [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.) to be cultured from two or more blood cultures drawn on separate occasions.⁸⁰ “Sameness” and “separate occasions” are defined in the NHSN document.

Epidemiology of central line-associated bloodstream infections

CRBSI epidemiology differs among ICUs and countries. In the most recent NHSN publication from 2015, median incidence densities (IDs: episodes per 1000 device-days) were as follows: 0.8 CLABSI episodes/1000 catheter-days for cardiothoracic ICUs; 1.1-1.2 episodes/1000 for medical ICUs; 1.4 episodes/1000 for trauma ICUs; 2.9 episodes/1000 for burn units; and 0.3-1.3 episodes/1000 for paediatric ICUs.⁸⁶ A UK study observed lower CRBSI IDs among non-teaching compared to teaching hospitals (2.8/1000 catheter days and 5.4/1000 catheter days, respectively).⁶¹ These data most likely reflect dissimilarities among the case mix between the hospital types. ICUs in developing countries have much higher CLABSI rates compared to high-income countries.²⁹ The recent INICC report identified an ID of 4.8/1000 device-days in 465 ICUs from 43 countries by using the NHSN CLABSI definitions.⁸⁷

CRBSI IDs are thought to be highest among ICUs. However, similar CRBSI rates were found in non-ICU units.^{35,88,89} Although the CVC utilisation ratio was much higher in the ICU (29.8/100 patient-days) compared to non-ICU units (5.0/100 patient-days) at HUG, the number of cumulative catheter-days was much higher in non-ICU units (60% [2140/3567]).³⁵ This study by Zingg and colleagues was the pilot study of a hospital-wide intervention study (see below)⁴⁵ and one of the few at the time to provide data of CVC-use and CLABSI in non-ICU settings.³⁵ The objective was to assess the situation regarding CVC insertion and use at HUG, a large primary and tertiary care centre. The results showed that CRBSI rates in non-ICU settings are similar to the ICU. CRBSI IDs for ICU, internal medicine, surgery and abdominal surgery were 5.6, 1.9, 2.4 and 7.7 per 1000 CVC-days at risk, respectively.

CRBSI IDs among children are higher than in adults (9–11 episodes per 1000 catheter-days), particularly in neonates.^{15,82,90-92} Neonates have specific types of intravascular lines, such as umbilical venous or arterial catheters or peripherally-inserted central venous catheters (PICCs), and thus, CRBSI IDs and risk factors can hardly be compared to adults.⁸² Classic non-tunnelled CVCs are used less often in neonates and small infants, mainly because insertion through the subclavian or jugular vein is complicated and requires general anaesthesia.

The epidemiology varies also with the type of catheter. Maki and colleagues published a meticulously performed review about CRBSI as a function of catheter type in adults.⁵⁶ The IDs for CVC, PICC, tunnelled CVC, peripheral venous catheters, and implantable port systems were 2.7/1000 catheter-days, 2.1/1000, 1.6/1000, 0.5/1000, and 0.1/1000, respectively. PICC lines are often perceived as a safe alternative to non-tunnelled CVCs. However, the performance of such lines is not superior to non-tunnelled CVCs if they are used for the same purpose as was evidenced in a recent non-randomized.⁹³ IDs between 638 CVCs and 622 PICC lines were 2.4/1000 and 2.3/1000 device-days, respectively.⁹³

Risk factors for central line-associated bloodstream infections

Various risk factors for CRBSI upon insertion, catheter handling, and work organisation have been described in the literature.^{53,94} Extrinsic risks such as the choice of the insertion site, the number of lumens, the catheter dwell-time, or nutritional intake can be (within limits) modified and thus, are candidates for a (multimodal or multidisciplinary) intervention strategy. Intrinsic risks cannot be modified, i.e., inherent risk factors of the patient. Protecting patients with intrinsic risk factors from adverse events related to medical devices relies on the proper indication and selection of the appropriate device.

Table 1: Modifiable risk factors for catheter-associated bloodstream infections^{53,94}

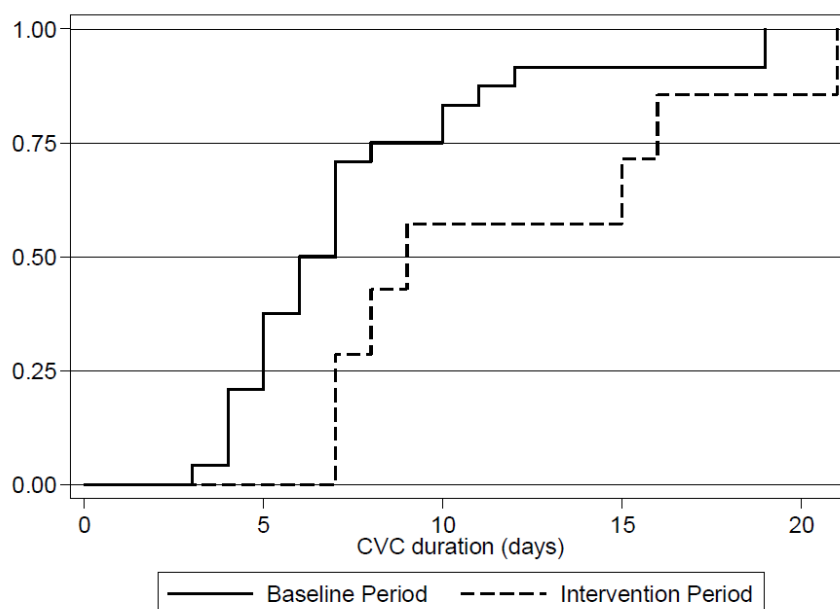
Risk factor	References	Validity	Quality improvement
Dwell-time	95	NCC	Catheter removal as soon as possible
Femoral access site	95-97	RCT	Femoral access site should be avoided
Guidewire exchange	98,99	RCT	No guidewire exchange if CRBSI is suspected
Multi-lumen catheters	100	NCC	Single lumen catheters should be preferred
Catheter-related thrombosis	101-103	NCC	Prophylactic anticoagulation or heparin-coated catheters
Parenteral nutrition	82,104,105	NCC	Encouraging enteral feeding
Reduced nutritional energy intake	106,107	RCT, PPS	Diminishing nutritional risk; optimising energy supplementation
Unfavourable nurse-to-patient ratio and high workload	94,108-111	NCC, CSS	Improving nurse-to-patient ratio
High proportion of pool or agency nurses	94,112,113	NCC	Reducing employment of agency nurses
Positive organisational culture and safety climate	94,114-116	QRS	Improving the organisational culture (leadership, pathways, work satisfaction)

CRBSI: Catheter-related bloodstream infection; CSS: cross-sectional study; NCC: non-controlled cohort study; PPS: point prevalence survey; QRS: qualitative research study; RCT: randomised controlled trial

Catheter dwell-time

CRBSI risk increases with CVC duration.^{82,117} Time-to-infection is shorter in non-tunnelled catheters^{95,118} compared to tunnelled catheters or implantable port-systems.¹¹⁹ The ID in the latter is lower, but the overall proportion of CRBSI is higher in long-term devices.¹²⁰ In two studies, Zingg and colleagues showed that the risk of dwell-time is not linear or exponential, but follows an s-shaped curve with little risk in the first few days, followed by a rapid upsurge, and little further increase thereafter (Figures 5-6).^{45,82,117} In a recent CRBSI prevention study at HUG, dwell-times between 7 and 12 days were independently associated with CRBSI, while shorter and longer durations were not.⁴⁵ Thus, CVCs should not be replaced routinely.^{81,98}

Figure 5: Time to central venous catheter-related bloodstream infection between baseline and intervention — prevention strategy targeting hand hygiene and catheter care on the incidence of catheter-related bloodstream infections; University Hospital of Zurich.¹¹⁷

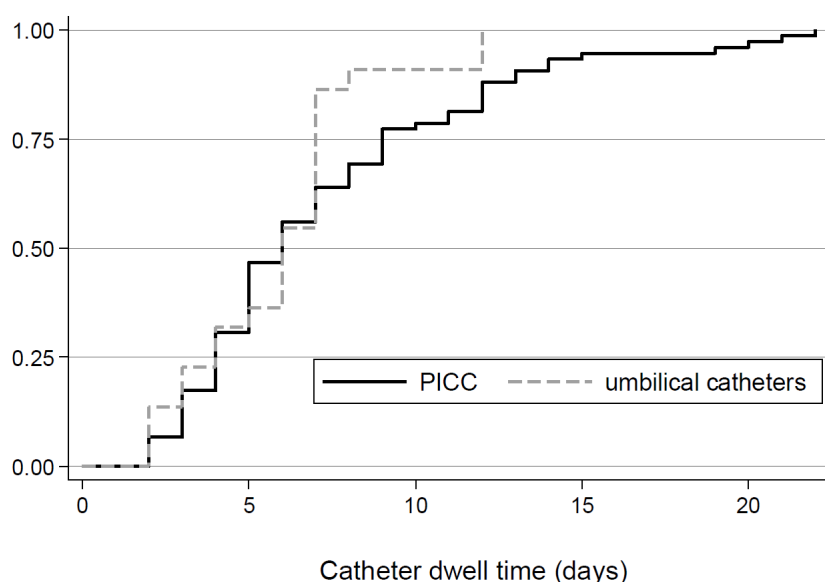


CVC: central venous catheter (Published in Zingg et al.¹¹⁷)

In a prospective 8-year surveillance study at HUG, Zingg and colleagues reported that dwell-time of central lines in neonates is a risk, but mainly in the first 7 days and that there was no

difference between umbilical lines and PICC lines (Figure 6).⁸² The study analysed 1,124 neonates with 2,210 central lines for a total of 12,746 catheter-days. Catheter dwell time was associated with central line-associated bloodstream infection and clinical sepsis for all umbilical catheters (OR [CI95%]: 1.2 per day of use [1.1–1.3]; $P<0.001$) and for PICCs for up to 7 days (OR [CI95%]: 1.2 [1.1–1.4]; $P=0.041$), but not thereafter (OR [CI95%]: 1.0 [0.9–1.1]; $P=0.90$).⁸²

Figure 6: Time to infection for peripherally-inserted central catheters and umbilical catheters among neonates — University of Geneva Hospitals, 2001–2008.⁸²



PICC: Peripherally inserted central catheter (Published in Zingg et al.⁸²)

Femoral access

The subclavian vein is superior to other access sites^{96,97,121} and is the preferred CVC insertion site. Although access through the internal jugular vein access may be more favourable to avoid local mechanical complications,¹²¹ the subclavian vein is still promoted as the preferred insertion site.^{81,122} Until recently, both jugular and subclavian access are accepted as being at similar risk for CRBSI and prevention programmes promote avoiding the femoral access site.^{123,124} However, a recent large and randomized multicentre study identified the subclavian access as significantly more favourable to the femoral and jugular

access, which performed similarly.¹²⁵ The femoral vein was not found to be an independent risk in a large CRBSI prevention study performed at the University Hospital of Zurich by Zingg and colleagues,¹¹⁷ and a randomized multicentre study in France comparing the jugular and femoral access of haemodialysis catheters did not find significant differences of CRBSI between the two access sites either.¹²⁶

Guidewire exchange

Guidewire exchange is common practice for catheter change, but should be avoided if CRBSI is suspected.⁹⁸

Multi-lumen catheters

The use of multi-lumen catheters was identified as a risk for CRBSI in one study,¹⁰⁰ but not in others.^{45,96,117} Whether the initially identified risk is a result of the calibre of the catheter or is due to more frequent access to the multiple lumens needs to be determined.

Thrombosis

A French study with very high numbers of internal jugular and subclavian vein thrombosis (42% [95% CI: 34-49] and 10% [95% CI: 3- 18], respectively) identified a 2.6-fold risk increase for catheter-related sepsis in the case of thrombosis.¹⁰¹ The findings were supported by two studies from a group in Tunisia reporting on the prevention of thrombosis and CRBSI by heparin-infusions and (later) the use of heparin-coated catheters.^{102,103} Thrombosis as a risk has disappeared from the literature, possibly due to an emphasis on the correct placement of CVCs where the tip lies within the superior cava vein above its junction with the right atrium (above the carina).¹²⁷ Today, the major problem in the context of thrombosis (and potential CRBSI) comes from PICCs.¹²⁸

Parenteral nutrition

Parenteral nutrition (PN) was repeatedly described as a risk factor for CRBSI, especially with long-term CVCs.^{82,104,105,129-131} Various *in vitro* studies tested the growth of microorganisms in single compounds of PN, in total PN (TPN), or in total nutrient admixtures (TNA). The growth of twelve different pathogens (*S. epidermidis*, *S. aureus*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Flavobacterium* spp., *S. saprophyticus*, and *Candida albicans*) were tested in a representative TNA (17.6% glucose, 5% amino acids, 4% lipid; pH 5.6) and compared to a control solution (5% dextrose).¹³² At various temperatures, *C. albicans* and *S. saprophyticus* grew in TNA. The authors concluded that TNA was a poor growth medium for most pathogens.¹³² In another study, while lipid emulsion and broth grew all tested organisms (*Escherichia coli*, *Enterobacter cloacae*, *P. aeruginosa*, *S. aureus*, and *C. albicans*), only *C. albicans* was found to proliferate in TPN.¹³³ *C. albicans* demonstrated significant growth regardless of fat content (0% or 5%) in admixtures containing variable concentrations of dextrose in an *in vitro* study.¹³⁴ Gram-negative microorganisms, such as *K. pneumoniae*, *E. coli*, and *P. aeruginosa* were able to proliferate in TNA with glucose, amino acids, and lipid emulsion, but growth was impaired in conventional TPN without lipids.¹³⁵ *S. epidermidis* was not able to proliferate in any admixture tested; however, *C. albicans* grew well in all admixtures. A recent study showed that the proliferation of *S. epidermidis* was not only affected by adding lipids to TPN, but also depended on glucose concentration and total non-nitrogen energy.¹³⁶ Growth was also reduced by higher pH values (~8.4). *S. epidermidis* was cultured from 7 of 9 catheters after lipid infusion, but only from 3 of 13 catheters after glucose infusion ($p = 0.016$) in a rabbit model.¹³⁷ Lipid, but not glucose, solutions containing low protein levels (0.1%–1.0%) supported the survival and growth of *S. epidermidis*. The reason for enhanced growth in the context of lipid administration is not clear. A modulation of the proinflammatory cytokine response to *S. epidermidis* by lipids has been suggested.¹³⁸ In a *S. epidermidis* sepsis model of whole cord blood cells from healthy infants, IL-6, IL-8, and TNF- α expression of CD14+

cells were significantly enhanced upon addition of a 1% lipid formulation, while lower lipid concentrations had no remarkable effect. When glucose was added to whole cord blood cultures, a dose-dependent effect was demonstrated for IL-8 expression, but not for other cytokines.

Reduced energy intake

A recent randomised study among two tertiary care ICUs in Geneva and Lausanne suggests that the provision of sufficient energy intake prevents HAIs even if supplemental PN (SPN) must be used to achieve this goal.^{106,139} The concept is interesting and may be valid since a hospital-wide prevalence survey also found an association of reduced energy intake ($\leq 70\%$ of predicted energy needs) and overall HAI.¹⁰⁷

Unfavourable nurse-to-patient ratio, high workload and high proportion of pool nurses

Poor nurse-to-patient ratio or high workload in the ICU is a risk for CRBSI, which was reported by a number of studies in children and adults.^{94,108-111,140} Pool or agency nurses who worked on different wards as needs required were identified as a potential risk for BSI, especially CABSIs in ICUs.^{94,112,113}

Intrinsic risk factors

Apart from modifiable risk factors, patients may have intrinsic factors that put them at risk for CRBSI and other HAI. Such non-modifiable risk factors include immunosuppression, liver failure and severe trauma.⁵³ Although severity of life scores, such as SAPS II or APACHE, at admission or co-morbidity indexes, such as the Charlson index, are useful prognostic tools, they are not independent from extrinsic risk factors for CRBSI and should not be used to justify high CRBSI rates.^{45,117,141} Male gender (2.54 [CI95%: 1.05–6.18]) and medical ICU stay compared to surgical and trauma ICU stay (3.32 [1.46–7.55]) were identified as independent risk factors in the Zurich ICU study by Zingg and colleagues.¹¹⁷

Diagnosis of central line-associated and central line-related bloodstream infections

Clinical findings alone have poor specificity and sensitivity in CRBSI diagnosis.^{142,143} Clinical signs must be combined with microbiological methods, which can be divided into two categories: 1) techniques requiring CVC removal; and 2) CVC-sparing methods.⁵³

Techniques requiring CVC removal

The roll-plate catheter technique by Maki is the best known semi-quantitative method.¹⁴⁴ The distal segment of the catheter (5 cm) is cut and rolled at least four times on a blood agar plate, which is then incubated overnight. A count of 15 colony forming units (CFU) or more is considered a positive result. This method has become the standard technique for CRBSI diagnosis. However, the test detects pathogens only on the external surface. Therefore, the roll-plate catheter technique is reliable only for short-term catheters (e.g., in the ICU), where colonization of the external surface is thought to be more important than biofilm formation in the lumen. Sensitivity and specificity for CRBSI diagnosis are 45–85% and 85%, respectively. To obtain organisms not only from the external surface, but also from the lumen, the catheter can be flushed with broth.¹⁴⁵⁻¹⁴⁷ A sample of the broth is placed on agar plates, which are incubated overnight. A count of more than 1000 CFU is considered to be a positive result. Organisms can be removed more vigorously from external and internal surfaces when sonication or vortexing is used.^{146,148,149} Catheter tips are placed in broth- or physiologic sodium chloride-containing containers. These are sonicated or vortexed and 100 µl of broth or sodium chloride are placed on blood agar plates and incubated overnight. A count of more than 100 CFU is considered to be a positive result. Further adjustment can be achieved when the length of the catheter segment is measured and the results are reported as CFU/cm (as done at HUG). Sonication has the disadvantage that the release of microorganism from the biofilm is quite vigorous and relevant organisms may be killed during this process. Routine screening of catheter tips may produce positive test results in asymptomatic patients. Thus, positive results from routine screening should be interpreted with caution and always taking into account clinical aspects of the patient. This is particularly

important when skin contaminants are isolated from a catheter tip because most CVCs are colonized with such microorganisms, even when in place only a short time.¹⁵⁰ However, the presence of true pathogens, particularly *S. aureus*, should prompt empiric antimicrobial treatment, even in the absence of positive blood culture tests or without clinical signs of infection.¹⁵¹ Catheter tips can be stained with acridine orange and examined directly under the microscope.^{152,153} Such staining is sensitive (84%) and specific (99%) for the detection of microorganisms, but it is not easy to perform in daily routine.¹⁵³

CVC-sparing techniques

The development of accurate techniques for CRBSI diagnosis without catheter removal would be most appreciated because febrile episodes in a patient with a CVC are frequent, but often do not translate into CRBSI. When blood is sampled simultaneously (<10 minutes apart) through the catheter and from a peripheral vein, such paired blood cultures can be compared quantitatively using either an absolute CFU count per volume or the differential time-to-positivity.¹⁵⁴⁻¹⁵⁸ In the differential time-to-positivity method, the two blood samples are placed together in an automatic culture detector recording every 15 minutes whether the sample is positive according to fluorescence changes related to microbial growth. If the time difference to positivity between the two samples is two hours or more and the catheter sample becomes positive first, BSI is likely to be catheter-related. For short-term catheters, this method has a sensitivity and specificity of 89% and 87%, respectively; for long-term catheters, sensitivity and specificity are 90% and 72%, respectively.¹⁴³ Positive laboratory results depend largely on the bacterial load and the microorganism responsible for CRBSI with polymicrobial CRBSIs most likely to be detected.¹⁵⁹ The problem with all methods using some microbiological culture technique is a false-negative result when there is concurrent antibiotic therapy at the time of blood culture sampling. Unfortunately, only few studies disclose this information and there are no data at all for antimicrobial-coated catheters. Such information would be much appreciated because existing definitions of catheter colonization and CRBSI might need to be modified when impregnated catheters are used. The acridine

orange leucocyte cytospin test is an alternative to conventional microbiological techniques. The test has the advantage of reporting data within 30 minutes with high sensitivity (87%) and specificity (94%).^{160,161} The sensitivity can even be pushed to 96% if positive test samples are additionally Gram-stained. Despite high performance and good feasibility, the test is not widely used. A new and more sophisticated method is the quantitative 16S ribosomal DNA detection test. The first blood volume, which is usually discarded before blood is collected from the CVC, serves as a sample for DNA isolation.¹⁶² Bacterial 16S ribosomal DNA is amplified and a concentration of >0.5 pg/ml blood has a high positive predictive value for CRBSI in a febrile patient.

Bouza and colleagues have compared three methods of CRBSI detection in a prospective randomised study in a single centre ICU: 1) semi-quantitative cultures from hub and skin at the insertion site; 2) differential quantitative blood cultures; and 3) differential time to positivity.¹⁶³ By taking into account convenience, use of resources and expertise, the study group recommended combining semi-quantitative superficial cultures and peripheral vein blood cultures, leaving differential quantitative blood cultures as a confirmatory and more specific technique.¹⁶³

Surveillance of performance and outcome indicators

Indicators should be clear and concise; action focused; important (stakeholders agree that the indicator makes a relevant contribution to respond to a problem); measurable (collecting meaningful and credible data); simple; acceptable to stakeholders; valid (accurately measure what they claim to measure); reliable (consistent over space and time); sensitive for change (detects change over time and across settings); and free from bias (no systematic errors).^{164,165} IPC surveillance activity distinguishes between performance and outcome indicators.

Performance indicators

Performance indicators have the advantage that sampling is less time-consuming and large numbers of events are produced allowing discrimination over time. Adherence to CVC insertion practice by applying a checklist (use of maximal sterile barrier (MSB) precaution measures at insertion and use of an appropriate skin antiseptic) and monitoring of hand hygiene compliance by direct observation are useful performance indicators in a CRBSI prevention programme.¹⁶⁶

Outcome indicators

Surveillance of outcome indicators, such as laboratory-confirmed BSI or CRBSI, is more time-consuming because clinical data must be obtained from patient charts.^{7,9,12,69-73,75-78}

NNIS has set the reference in the field many years ago by establishing prospective outcome surveillance in US ICUs.^{6,7} This concept was later adopted by national and international surveillance networks.^{11,12,167} In the absence of electronic patient records, outcome surveillance is time-consuming and thus hospital-wide all-HAI surveillance is never performed. Most hospitals focus on risk areas and/or confine surveillance to some indicator infections. For example, national surveillance activities focus on SSI in Switzerland¹⁶⁸ or very specific outcomes, such as MRSA BSI in England.²¹ CLABSI/CRBSI is one of the recommended outcome measures by the US HICPAC (Hospital Infection Control Practices Advisory Committee)¹⁶⁹ and has become one of the most commonly performed outcome indicators. This is due to the simplicity of case-finding (automated by screening microbiological data) and the fact that central lines are often accurately documented.¹⁷⁰ Future electronic data records will help to improve surveillance by using more screening algorithms.

Outcome of catheter-associated bloodstream infections

The impact of CRBSI on patient morbidity and mortality and hospital resources has been a subject of debate since many years. The association with excess length of hospital stay is

clearly established. However, attributable mortality rates range from 2% to 25% and thus either over- or underestimates the true rate.^{53,171,172} It is accepted that CRBSI is associated with costs, but numbers vary from US\$ 3,000 to US\$ 40,000 per CRBSI case.⁵³ Unfortunately, the value of cost-effectiveness studies is often limited due to lack of transparency, narrow economic perspectives, and poor methodological quality.¹⁷³ Catheters causing CRBSI must be removed unless the incriminating pathogen is a skin commensal or an *enterococcus*.¹⁷⁴ This is especially true for short-term catheters since their removal usually resolves the problem. However, CRBSI among long-term tunnelled catheters may successfully be treated without catheter removal in specific situations and when skin contaminants are involved.¹⁷⁵

Table 2: Attributable mortality, length of stay, and costs of central line-associated or -related bloodstream infections.⁵³

Author	Year of publication	Reference	Attributable mortality	Attributable length of stay	Attributable costs (US\$)
Pittet	1994	¹⁷²	25%	24	41,000
Soufir	1999	¹⁷⁶	25%	-	-
Digiovine	1999	¹⁷⁷	4%	7	17,000
Rello	2000	¹⁷⁸	13%	20	4,000
Pelletier	2000	¹⁷⁹	14%	-	-
Renaud	2001	¹⁸⁰	12%	9.5	-
Rosenthal	2003	¹⁸¹	25%	12	4,900
Blot	2005	¹⁷¹	2%	12	14,000

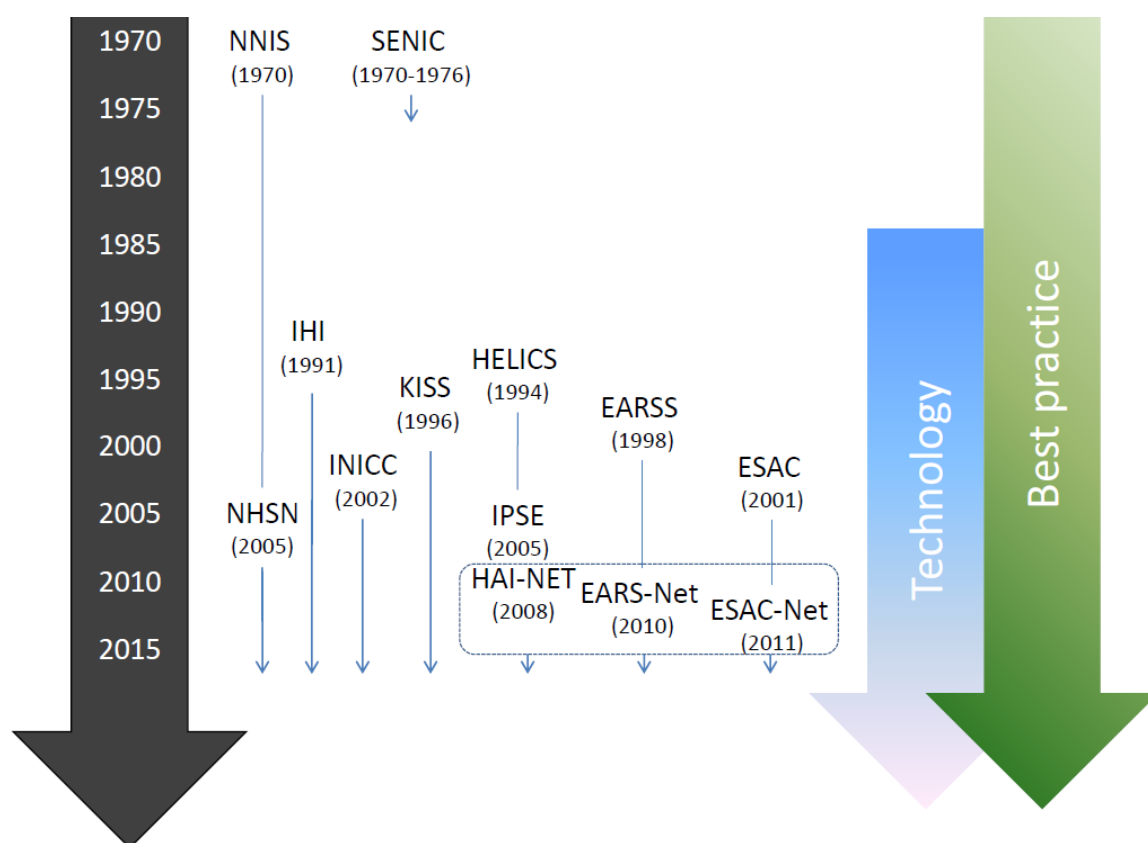
(Published in Zingg et al.⁵³)

History of the prevention of healthcare-associated infections

The prevention of HAI goes back centuries. In 1849, Semmelweis significantly reduced the rate of puerperal sepsis in Vienna, Austria, by introducing a chlorinated lime solution for hand hygiene.¹⁸² What we call “modern” IPC is based on the work of the pioneering SENIC (Study on the Efficacy of Nosocomial Infection Control) project, initiated in the 1970s by the

CDC.^{7,183} The method was based on patient data from 338 US hospitals. HAIs were detected by thorough patient chart review in repeated point prevalence surveys. The HAI prevalence for USA at that time was estimated at 5.2%.^{7,184-187} Hospitals that have employed a trained IPC physician, IPC nurses (one per 250 beds), and established a system to report infection rates have reduced HAI by about 32%.¹⁸⁸ Figure 7 summarizes the milestones in the evolution of modern IPC.

Figure 7: The history of “modern” infection prevention and control



EARSS: European Antibiotic Resistance Surveillance System; EARS-Net: ECDC European Antibiotic Resistance Surveillance Network; ECDC: European Centre for Disease Prevention and Control; ESAC: European Surveillance of Antibiotic Consumption; ESAC-Net: ECDC European Surveillance of Antibiotic Consumption Network; HAI-Net: ECDC Healthcare-associated Infection Network; HELICS: Hospital in Europe Link for Infection Control through Surveillance; IHI: Institute for Healthcare Improvement; INICC: International Infection control consortium; IPSE: Improving Patient Safety in Europe; KISS: Krankenhaus Infektions Surveillance System; NHSN: National Healthcare Safety Network; NNIS: National Nosocomial Infection Surveillance; SENIC: Study on the Efficacy of Nosocomial Infection Control.

Prevention of central line-associated bloodstream infections

For a long time, CLABSI prevention was the domain of technology.¹⁸⁹ Studies in the past addressed tunnelling of catheters, antiseptic ointments, impregnation of catheters, change to needleless access devices, various skin antiseptics, and antiseptic dressings.¹⁹⁰ Technology has become less visible in the past years, although the effectiveness of lock solutions and skin antiseptics was further explored and catheter impregnation may not yet have reached its limit. A new concept of HAI prevention is optimized nutritional energy intake.^{106,107,139} Best practice interventions to improve procedures have gained importance in the past years.^{53,189,190} CRBSI prevention can be stratified into technology, optimized nutritional energy intake, and best practice interventions.

Technology

Technology is not a stand-alone in the prevention of CRBSI and some products are considered as part of “best practice” and incorporated in bundle interventions.^{124,190,191} The “artificial” distinction of discussing technology lies in the study methods that were used to test the effectiveness of a series of medical devices or pharmaceutical products. Many studies were performed at a time when behavioural change interventions for practice improvement were not yet widely accepted as the most powerful strategy in HAI prevention.

Chlorhexidine-gluconate

Skin antisepsis with chlorhexidine-gluconate (CHG) has been repeatedly shown to be superior to the use of povidone-iodine.^{192,193} CHG has become an indispensable part of many CLABSI prevention “bundles”.¹⁹⁰ The first studies were done using an aqueous 2% product.¹⁹² Later studies turned to 0.5% CHG in 70% alcohol,^{191,194} whereas most studies promoting CHG use as part of a bundle strategy neither disclosed the CHG concentration nor whether the product was alcohol-based or not. Thus, the role of CHG may have been overestimated in the past.^{195,196} Some of the more recent best practice intervention studies used alcohol-based 2% CHG.¹⁹⁷⁻²⁰⁰ The most important factor in terms of effective skin

antisepsis is the combination of alcohol (preferably isopropanol) and a substance with remanent effectiveness, such as CHG, iodine or octenidine.

Impregnated catheters

Impregnating catheters has a long tradition in the literature of CRBSI prevention. Despite abundant literature on this topic, impregnated catheters are not used consistently.²⁰¹ Many studies testing impregnated catheters were of poor quality and only a few (7 of 24) included catheter with dwell-times of more than 12 days.²⁰² This is of importance as the effectiveness of CHG–silver sulfadiazine (CHG/SS) only lasts for approximately 1 week.²⁰³ Quite inconsistently with this evidence, the EPIC guideline recommended antimicrobial CVCs for adult patients who require central venous access for 1–3 weeks.²⁰⁴ Similarly, the former HICPAC recommended the use of antimicrobial CVCs when catheters are expected to remain in place for more than 5 days.¹²² Antibiotic-coated catheters (minocycline-rifampicin) have been shown to be more effective than CHG/SS CVCs and to significantly reduce CRBSI. A recent meta-analysis analysing minocycline-rifampicin-impregnated catheters in 8 randomised controlled trials calculated an impressive CRBSI reduction of more than 75%.²⁰⁵ Most of the studies included in the meta-analysis were sponsored by industry and thus, bias cannot be excluded. The pooled CRBSI incidence of the control groups was 4.5%, which is above the standard of care accepted in high-income countries today. The effectiveness of CHG/SS catheters may be limited by improved compliance with best practice procedures. A prospective single-centre study reduced CLABSI rates by improving best practice in catheter handling and by using CHG/SS catheters.²⁰⁶ After switching back to standard non-impregnated catheters there was no increase in infections (CHG/SS CVCs to standard CVCs: 0.5/1000 vs. 0.8/1000 catheter-days).²⁰⁶ Anti-infective catheters should not be recommended for prolonged catheter dwell-times, but only when CLABSI rates are above the institutional goal, despite establishing best practice.^{81,207}

Chlorhexidine-impregnated dressings

A randomised multicentre trial in France achieved significant CRBSI reductions after the use of CHG-impregnated sponges.²⁰⁸ The rates decreased from 1.3/1000 catheter-days to 0.4/1000 (hazard ratio [HR]: 0.24 [95% CI: 0.09–0.65]). A follow-up with a CHG dressing confirmed the results of the previous study.²⁰⁹ CHG-impregnated sponges were effective also in oncology where CVCs were in place for a prolonged time (control CVCs and intervention CVCs: 15.8 days and 16.6 days, respectively).²¹⁰ The CRBSI IDs decreased from high 7.2/1000 device-days to 3.8/1000 ($P=0.02$).

Lock solutions

Lock solutions serve either therapeutic or preventive purposes. For therapeutic use, the most recent clinical practice guidelines issued by the Infectious Diseases Society of America (IDSA) recommend antibiotic lock therapy for catheter salvage in uncomplicated CRBSI due to CoNS and enterococci.¹⁷⁴ A novel lock solution using a combination of 7% sodium citrate, 0.15% methylene blue, 0.15% methyl-paraben, and 0.015% propyl-paraben performed well in patients with haemodialysis catheters.²¹¹ The 201 catheters that were locked with this product were significantly less at risk for CRBSI compared to the 206 controls that were locked with unfractionated heparin (0.24 vs. 0.82 per 1000 catheter days; $P=0.005$). Ethanol locks have been promoted as a simple means to prevent CLABSI. The substance works well *in vitro*^{212,213} and the results in patients with long-dwelling catheters were favourable.^{214,215} However, two recent large randomised controlled trials did not find significant efficacy for CRBSI prevention.^{216,217} The reasons for this are not clear. One study applied a high ethanol concentration (70%), but during a short incubation time (15 minutes);²¹⁷ the other study applied a low concentration (50%) during a prolonged incubation time (2–3 hours). The successful studies in patients with long-dwelling catheters used high ethanol concentrations (70%) during long incubation times.^{214,215} Thus, the negative results of the large randomised trials may have been due to limitations of the methodologies. The substance may have additional limitations. A recent systematic review identified a number of potential hazards

with ethanol locks, such as structural changes of catheters *in vitro*, elution of molecules from the catheter polymers *in vitro*, systemic toxicity in clinical studies, increased catheter occlusion in clinical studies, and breaches in catheter integrity in clinical studies.²¹⁸ Urokinase was repeatedly reported to be a successful salvage therapy in children with tunnelled long-dwelling catheters,^{219,220} and was recently proposed as CRBSI prevention strategy.²²¹ However, it was only effective for CoNS in adults and further studies are required to provide proof of the efficacy and safety of urokinase in this area.

Bathing patients with chlorhexidine

Daily bathing of ICU patients with CHG cloths has reduced bacteraemia due to vancomycin-resistant enterococci in an ICU²²² and a long-term care facility.²²³ The results were confirmed in a cross-over cluster-randomised trial in 9 ICUs,²²⁴ although HABSIs rates during control and intervention periods were high (6.6/1000 vs. 4.8/1000 catheter-days, respectively). A cluster-randomised study in 43 hospitals with 74 ICUs tested three interventions: 1) screening and isolation of MRSA patients (without further measures); 2) targeted decolonisation of identified MRSA patients; and 3) universal decolonisation with mupirocin and CHG body wash of all ICU patients. BSI from any pathogen decreased most significantly by using the above-mentioned third intervention (6.1 vs. 3.6/1000 catheter-days, respectively). Even in neonates, CHG bathing was effective.²²⁵ CLABSI rates only decreased in the population eligible for bathing (birth weight >1000g and/or age ≥28 days), but not in others. As CHG is used for hand hygiene, preoperative skin preparation, and now bathing patients in the ICU,^{222,226,227} extensive use of this substance may result in resistance.²²⁸ Thus, there is a need to test alternative substances. Octenidine (0.1%) in propanol/isopropyl alcohol significantly reduced catheter-tip colonisation compared to ethanol/propanol (7.9 vs. 17.8%; $P=0.009$) in a randomised controlled trial.²²⁹ Unfortunately, the comparator product contained alcohol only and, thus, no conclusion can be made about its competitiveness to standard alcohol-based 2% CHG, which is the widely recommended substance.

Ultrasound guidance

Ultrasound-guided catheter insertion has been found to reduce CRBSI proportions (from 16% to 10%) compared to the so-called “landmark” technique.²³⁰ A large study, which was recently performed at HUG, was not able to find a significant difference of CLABSI between the landmark technique and the use of ultrasound.^{231,232} This is most likely due to consequent training of staff in correctly using the technique.²³² The CLABSI proportion in the Geneva study was 1.9% (incidence density: 2.1/1000 device-days). This is much lower, and closer to the reality of most acute care hospitals in high-income countries, compared to the very high numbers of the initial trial. Ultrasound was initially intended to prevent mechanical complications such as multiple punctures, arterial puncture, or pneumothorax.²³³ The role of ultrasound guidance in the context of CABSIs is not clear. The use of an additional device, such as ultrasound, may complicate CVC insertion and set the stage for breaches in aseptic non-touch technique, but fewer venous punctures and a shorter insertion time may counterbalance the risk for infection.²³¹ The study at HUG was able to show that under real conditions in a high-income country, ultrasound neither protects against CABSIs, nor does it represent a risk factor.^{231,232} New aspects, such as the introduction of ultrasound for CVC insertion, must be discussed between operators and IPC professionals in order to make sure that safety is maintained. Ultrasound for CVC insertion has now become part of the multimodal training of doctors in the skills’ laboratory at HUG.

Optimized nutritional energy intake

Optimized energy intake is a novel concept in HAI prevention and not yet adopted. A randomised study in two tertiary care ICUs in Geneva and Lausanne evidenced that SPN reduced HAI in the longer run of ICU stay.¹⁰⁶ Given the evidence that PN is a risk factor for CRBSI, this finding was unexpected. During the first days when SPN was applied to provide adequate energy needs (for 5 days after an initial phase of 4 days enteral nutrition only), there was no difference in HAI. However, after SPN was terminated (from day 9) – and without further PN – less HAIs were detected (hazard ratio [HR] [95% CI]: 0.65 [0.43-0.97];

$P=0.03$). The effect was mainly shown for VAP but there were less CRBSI as well. The role of optimized energy intake on HAI was tested hospital-wide in a recent prevalence survey at HUG.¹⁰⁷ Dietary intake was assessed for one day among all inpatients receiving three meals per day. Nutritional risk was assessed using Nutritional Risk Screening (NRS)-2002, and defined as a NRS score ≥ 3 . Energy needs were calculated using 110% of Harris-Benedict formula. HAIs were diagnosed by using the CDC criteria. From 1689 hospitalised patients, 1024 were eligible for the measurement of energy intake. HAI prevalence was 6.8%. Energy intake $\leq 70\%$ of predicted energy needs was associated with HAI (odds ratio [OR] [95% CI]: 2.26 [1.24-4.11]; $P=0.008$).¹⁰⁷ Insufficient dietary intake can be perceived as a risk factor for HAI and optimized nutritional energy intake is a new area in the field of IPC and nutrition may be taken into the equation of HAI prevention in the future.

Best practice procedures

“Best practice procedure” is a wide category embracing improved procedures and technology, together with the ultimate goal to change the behaviour of healthcare workers and encourage them to be in line with effective evidence-based practice. The concepts of multimodality and multidisciplinary fall into this category, but also play a role in implementation research.

Appropriate indication

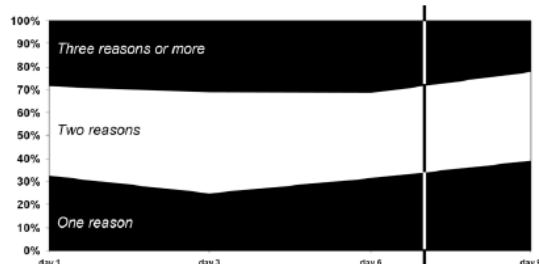
Any indication for a CVC insertion must be justified and catheters should be removed as soon as they are no longer required.⁵³ In a second pilot study, Zingg and colleagues aimed to understand why and how CVCs were used at HUG.³⁴ At insertion and every third day thereafter, patients with a CVC were visited and healthcare workers on the ward were asked about the reasons for CVC use. A total of 378 CVCs accounting for 2704 catheter-days were prospectively observed in the entire hospital. Most CVCs were used for prolonged antibiotic therapy followed by parenteral nutrition (Figure 8). While CVCs in the ICU were used for more concomitant indications but for shorter dwell-times (Median [IQR]: 4 days [2-7]), CVCs

in non-ICU wards were used for less concomitant indications (mostly one single) but during a longer dwell-time (Median [IQR]: 8 days [3-15]). Based on the findings and the fact that IDs in the ICU and in non-ICU units were similar,^{26,34,35} one of the assumptions was that the most important risk factor for CRBSI is the number of accesses to the infusion system (many per day in the ICU [many manipulations during shorter dwell-time]; less per day in non-ICU units [few manipulations during longer dwell-time]). This study could not formally approve this hypothesis though and no other study up to this day ever did. The proportion of unnecessary CVC-days was lower than expected (4.8%). In 94% of cases, there was agreement among nurses and doctors on the reasons for CVC use. However, 35 on-site visits (8.3%) in non-ICU settings revealed that neither the nurse nor the treating doctor knew why the catheter was in place.³⁴

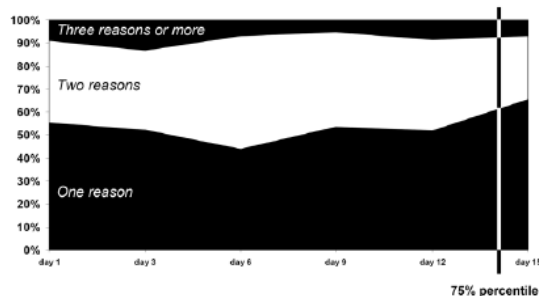
Figure 8: Specified indications for central venous catheter use during dwell-time, prospective catheter surveillance, University of Geneva Hospitals, 2009.³⁴

Number of „indications“

ICU; median dwell-time: 4 (2-7)

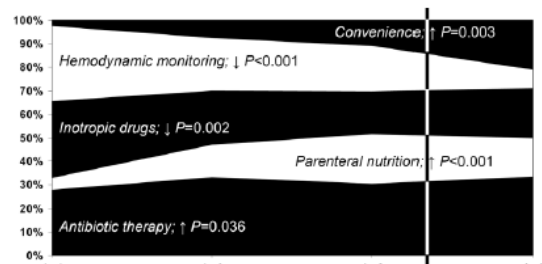


Non-ICU; median dwell-time: 8 (3-14)

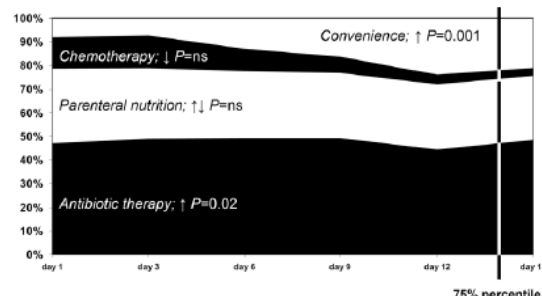


Types of „indications“

ICU; median dwell-time: 4 (2-7)



Non-ICU; median dwell-time: 8 (3-14)



↑ increase; ↓ decrease; ns: non-significant; P-values correspond to statistical testing for entire catheter dwell times (Adapted from Zingg et al.³⁴)

Catheter insertion

The benefit of a strict aseptic technique at catheter insertion was established many years ago.²³⁴ Standardised MSB precautions were effective in CRBSI prevention in the early 1990s^{235,236} and are part of many CRBSI prevention strategies in ICUs today.^{123,124,191,237-239} MSB measures include wearing a surgical mask, cap, sterile gown, sterile gloves, and covering the insertion site with a large surgical drape. Interestingly, a recent randomised multicentre trial did not find MSB to be effective for CRBSI prevention (2.4/1000 vs. 1.9/1000; relative risk [RR]: 1.2; 95% CI: 0.43–3.1; $P=0.78$).²⁴⁰ The study was performed in surgical patients on general wards and median catheter dwell-times in both groups were high (14 days). The fact that the importance of MSB disappears with prolonged dwell-times is consistent with the findings of other studies, i.e., interventions at CVC insertion become less important with longer dwell-times compared to interventions targeting CVC care.¹¹⁷ Alcohol-based CHG and povidone iodine are the most frequently used skin disinfectants.^{123,124,191,208} Both are recommended by the CDC.^{81,122} CHG has been shown to be more effective than povidone iodine in early studies^{192,193} and, as described above, it has now become standard for skin preparation before CVC insertion and for CVC care.^{45,123,124,191} The subclavian vein is the preferred and recommended site of catheter insertion.⁹⁷ Hand hygiene is a key factor in the process of CVC insertion and sterile gloves must be worn.^{123,191,241} Adherence to the recommended steps of CVC insertion should be observed by using a checklist.^{123,242-244}

A hospital-wide CLABSI prevention programme at HUG addressed CVC insertion and –care by offering simulation training for doctors by their peers in skills’ laboratory workshops and an E-learning tool for nurses.⁴⁵ The intervention at CVC insertion included the introduction of fully equipped CVC insertion carts and ergonomic single use insertion kits. The kits were designed to follow the procedure sequence of aseptic skin preparation and CVC insertion; the first upper level contained the material for skin preparation, and the second level included all the necessary equipment for CVC insertion.⁴⁵ A detailed insertion checklist was defined by the study group based on evidence in the literature and by repeated practice testing in daily

routine. All measures mentioned above were taken into account. The workshop for doctors was divided into 3 sequences: 1) lecturing on CVC insertion and CLABSI prevention; 2) filming of participants inserting a CVC; and 3) giving feedback based on best practice recommendations. After the workshop, each participant had to perform at least one CVC insertion under supervision.⁴⁵

Catheter care

Most multidimensional and/or bundle studies focused on CVC insertion. However, catheter care has a similar impact to catheter insertion on the outcome.¹¹⁷ Catheter care interventions focus on aseptic technique, reducing colonisation at the insertion site by local disinfection, changing administration sets correctly (every 96 hours in patients not receiving blood, blood products, fat emulsions, or chemotherapy; within 24 hours when used to administer blood, blood products, or fat emulsions), covering the insertion site with appropriate dressings, and removal of the catheter when necessary.^{81,245-247} Today, the “correct” dressing for a CVC is a semi-permeable transparent dressing and a gauze dressing should be used only if the insertion site is bleeding or oozing (and only intermittently).²⁴⁸ Gauze dressings must be replaced every 2 days, while transparent dressings can be left in place 7 days unless the dressing becomes damp, loosened, or visibly soiled.⁸¹ The use of needleless access devices is controversial. While some authors support their use with the idea of having a closed system,²⁴⁹ others emphasize their risk, particularly when mechanical valves are used.^{250,251} Although dwell-time is a risk for CRBSI, CVCs should not be changed routinely. The risk by re-inserting a catheter (even using a guidewire) is considered to outweigh the risk of prolonged dwell-time.²⁰⁷ However, any catheter with suspected CRBSI²⁴⁷ or no clear indication for use must be removed.^{34,124,237,247} If skin commensals or enterococci are isolated from blood cultures, a CVC can be left in place and treated by antibiotic lock solutions.¹⁷⁴ By contrast, topical antibiotic ointments or creams at the insertion site are of no benefit and must not be used due to the risk of emerging resistance.^{247,252} All routine infusates and drugs must be prepared using strict aseptic technique.^{117,247,253,254} The use of PN should be minimized

and the duration shortened. PN should be compounded in the pharmacy under strict aseptic technique and, whenever possible, ready-to-use preparations should be used.¹²⁹

Only a few studies explicitly have addressed catheter care^{117,197,255-257} or combined the two together in a comprehensive manner.^{45,191,242,258} Zingg and colleagues tested a modular intervention to improve CVC care in 5 ICUs at the University Hospital of Zurich.¹¹⁷ The intervention did not interfere with CVC insertion practice or the selection of the skin antiseptic. This choice was deliberate because at the time when the study was performed, most CLABSI prevention studies focused on catheter insertion and promoted the importance of CHG for skin antisepsis. The aim of the study was to test exclusively a comprehensive CVC care programme which was divided into four modules: 1) hand hygiene, 2) catheter site dressing, 3) CVC manipulation by using a non-touch technique, and 4) aseptic preparation of infusates. The study analysed 999 patients accumulating 13,479 catheter-days, 6200 catheter-days in the baseline period and 7279 catheter-days in the intervention period. CRBSI decreased from 3.9/1000 catheter-days in the baseline period to 1.0/1000 in the intervention period ($P<0.001$). Time to CRBSI was significantly longer in the intervention period (median 9 days vs. 6.5 days, respectively; $P=0.02$). As one of few studies, performance indicators were measured: Compliance with hand hygiene improved slightly from 59% in the baseline period to 65% in the intervention period, but the rate of correct performance of the practice increased from 22.5% to 42.6% ($P=0.003$).¹¹⁷ A similar modular strategy was used for the “catheter care” part of the hospital-wide CLABSI prevention programme at HUG.⁴⁵ The training addressed 1) CVC insertion, 2) preparation of infusates and CVC manipulation, 3) dressing change, 4) CVC removal, and 5) clinical surveillance and documentation. Nurses were trained by their peers applying the train-the-trainer approach and using an E-learning platform (www.carepractice.net).

Multimodal prevention strategies

“Multimodality” as a term is not a stand-alone. “Multimodal” refers to action, which in IPC is the prevention of HAI. Eggimann and colleagues were the first to show the effectiveness of a comprehensive CRBSI prevention programme in a single centre ICU.^{191,259} They adapted their local guidelines to the evidence-base after scrutinizing the literature and offered hands-on training to doctors and nurses. Two years after a successful single centre pilot project,¹²³ Pronovost and colleagues conducted a multicentre CLABSI prevention programme in more than 100 ICUs in the US state of Michigan.¹²⁴ They promoted the use of five evidence-based procedures recommended by the CDC and identified as “having the greatest effect on CRBSI and the lowest barriers to implementation”:⁶⁰ 1) hand washing; 2) using full-barrier precautions during CVC insertion; 3) cleaning the skin with CHG; 4) avoiding the femoral access site if possible; and 5) removing unnecessary catheters.^{124,260} The selected procedures were later referred to as the CRBSI prevention “bundle”, a concept already successfully used for the prevention of VAP.²⁶¹ The terms “bundle” and “multimodal intervention strategy” have been used interchangeably, although this is not quite correct. Both have in common to promote best practice of a (complex) procedure at various levels, but while the bundle refers to the procedure only, the term multimodal contains the suffix “mode”, which refers to the “way” information is transmitted to professionals and thus, addresses implementation. The Pronovost study as published initially¹²⁴ is an example of a “bundle” promotion. Only his later “Explaining Michigan” paper shed light on the aspects of the dynamics of implementation emphasizing the “multimodality” aspects of the project.¹³

“Implementing infection control programmes following a multimodal strategy, including tools such as bundles and checklists developed by multidisciplinary teams, and taking into account local conditions” was identified as one of 10 key components of the so far largest systematic review aiming at defining key components of successful organisation and management of IPC.⁹⁴ This systematic review and expert guidance was initiated by the ECDC and performed by Zingg and colleagues in collaboration with three academic institutions (University of

Geneva Hospitals, Switzerland; Imperial College, London, UK; University of Hospital of Freiburg, Germany). Eight studies of sufficient quality and thus contributing to the evidence-base showed that multimodal strategies were helpful to prevent CRBSI.^{117,191,238,262-266} Seven were quantitative ICU studies^{117,191,238,262-265} and one was a qualitative study reporting factors of behavioural change in the context of peripheral venous lines.²⁶⁶ All intervention studies used a multimodal approach in which bundles or comprehensive procedures were defined and promoted at various levels. Three studies focused primarily on catheter insertion,^{238,262,263} one addressed catheter insertion and care,¹⁹¹ and one focused on catheter care alone.¹¹⁷ All seven quantitative studies showed CRBSI improvement. Four studies also provided data about process indicators.^{117,238,264,265} Many initiatives were based on the bundle strategy proposed by Berenholtz and colleagues,¹²³ and brought to attention to a large audience by Pronovost and colleagues.^{45,117,124,198,200,238,260,263,267,268} Some hospitals added additional practices, such as the introduction of needleless connectors, applying PN via multi-lumen CVCs,¹⁹⁹ or emphasizing correct hub disinfection before access to the infusion system.²⁴² Others focused on catheter care.^{117,197,199,242,267,269} The Zürich study by Zingg and colleagues was among the selected eight studies of sufficient quality.¹¹⁷ Table 3 is an update of the findings of a review about CLABSI prevention published by Zingg and colleagues in 2011.¹⁹⁰

Table 3: Multimodal strategies in the prevention of catheter-related or catheter-associated bloodstream infections.

Study (authors)	Setting	Practice interventions	Implementation strategies	Control/ intervention (N/1000 device-days)	BSI type
Apisarnthanarak ²⁶⁷	Hospital-wide, single centre	Hand hygiene; full barrier precautions at catheter insertion; CHG for skin antisepsis; avoiding the femoral insertion site; removal of unnecessary catheters; optimal catheter care	Lectures; posters; hand hygiene tests	14.0/1.4 (P<0.001)	CABSI
Bion ²⁷⁰	223 ICUs, multicentre	Hand washing; MSB at catheter insertion; checklist during catheter insertion; CHG for skin antisepsis; avoiding the femoral insertion site; CVC maintenance: aseptic access technique, daily site review, and removal of CVCs at earliest	Training days (data definitions, technical and non-technical interventions); Teleconference calls and internet-based teaching	3.7/1.5 (P<0.001)	CABSI

		opportunity			
DePalo ²³⁸	23 ICUs, multicentre	Hand washing; full barrier precautions at catheter insertion; CHG for skin-antiseptic; avoiding the femoral insertion site; removal of unnecessary catheters	CUSP	3.7/1.0 (P=0.003)	CABSI
Eggimann ¹⁹¹	1 ICU, single centre	Comprehensive intervention addressing material preparation, line insertion, dressing (change), CVC replacement, CVC care, CVC removal, hand hygiene	Slide-shows; practical demonstrations; bedside training	3.1/1.2 (P=0.04)	CLABSI
Guerin ¹⁹⁷	2 ICUs, single centre	Daily inspection of insertion site; site care in case of wet or soiled dressing; documentation of ongoing catheter need; hand hygiene before handling the intravenous system; alcohol scrub of infusion hubs before use	Practice training of catheter insertion; practice training of catheter care; tests	5.7/1.1 (P=0.004)	CABSI
Marra ¹⁹⁸	1 ICU, single centre	Hand washing; full barrier precautions at catheter insertion; central line cart; CHG for skin antiseptic; avoiding the femoral insertion site; removal of unnecessary catheters	Lectures; monthly feedback of bundle compliance	6.4/3.2 (P<0.001)	CABSI
Miller ²⁶⁹	29 PICUs, multicentre	Hand hygiene; CHG for children ≥2 months; insertion cart; insertion checklist; daily review of line necessity; optimized catheter-care	Support and promotion by senior ICU leader; involvement of quality improvement leaders; workshops; local practice adaptation	5.4/3.1 (P<0.001)	CABSI
Palomar ²³⁹	192 ICUs, multicentre	Hand washing; full barrier precautions at catheter insertion; checklist during catheter insertion; CHG for skin-antiseptic; subclavian vein as the preferred insertion site; removal of unnecessary catheters	CUSP; principles of engage, educate, execute, and evaluate	3.1/1.1 (P<0.001)	CRBSI
Peredo ²⁶³	2 ICUs, single centre	Checklist for catheter insertion; CHG for skin antiseptic; avoiding the femoral insertion site; removal of unnecessary catheters	Lectures	6.7/2.4 (P=0.015)	CRBSI
Perez ¹⁹⁹	3 ICUs, single centre	Full sterile sheet for catheter insertion; subclavian vein as preferred insertion site; needleless catheter connectors; 2% CHG for skin antiseptic; parenteral nutrition via a multi-lumen CVC; optimal catheter care	Lectures; before and after knowledge tests	4.2/2.9 (P=0.030)	CABSI
Pronovost ¹²⁴	90 ICUs, multicentre	Hand washing; full barrier precautions at catheter insertion; checklist during catheter insertion; CHG for skin antiseptic; avoiding the femoral insertion site; removal of unnecessary catheters	CUSP	7.7/1.1 (P<0.001)	CRBSI
Schulman ²⁴²	18 NICUs, multicentre	Hand hygiene; central line kit or cart for catheter insertion; MSB; checklist for catheter insertion; CHG for skin antiseptic; optimized catheter care; checklist for catheter care; daily evaluation of catheter exit site; aseptic technique for catheter handling; 'scrub the hub'; daily review of line necessity	State-wide workshops; periodic surveys and conference calls	3.5/2.1 (P<0.001)	CABSI
Venkatram ²⁶⁸	1 ICU, single centre	Hand hygiene; full barrier precautions at catheter insertion; checklist during catheter insertion; CHG for skin-antiseptic; preferring subclavian access; daily review of line necessity	Lectures	10.7/1.7 (P<0.001)	CRBSI
Weber ²⁰⁰	8 ICUs, single centre	Hand washing; full barrier precautions at catheter insertion; checklist for catheter insertion; customized CVC insertion kits; alcohol-based CHG for skin antiseptic; avoiding the femoral	Lectures; repeated practice training for CVC insertion and care	8.9/2.4 (P<0.001)	CABSI

		insertion site; removal of unnecessary catheters			
Zingg ¹¹⁷	5 ICUs	Hand hygiene; optimized catheter dressing; no-touch technique for CVC manipulation; preparation of infusates; optimized catheter care	Tool preparation guided; by frontline healthcare; workers' perceptions; bed-side training; lectures	3.9/1.0 (P<0.01)	CRBSI
Zingg ⁴⁵	Hospital-wide, single centre	Comprehensive intervention addressing CVC insertion, CVC care (dressing change, preparation of drugs/infusates), CVC removal, hand hygiene	Skills' laboratories training for doctors; modular E-learning using a train-the-trainer system for nurses; optimized insertion set; trolleys for CVC insertion	2.3/0.7 (P<0.001)	CLABSI

CHG: Cchlorhexidine-gluconate; CLABSI: central line-associated bloodstream infection; CRBSI: catheter-related bloodstream infection; CUSP: comprehensive unit-based safety programme; CVC: central venous catheter; ICU: intensive care unit; MSB: maximal sterile barrier; NICU: neonatal intensive care unit; PICU: paediatric intensive care unit

(Updated from Zingg et al.¹⁹⁰)

Most published CRBSI prevention studies were conducted in the ICU. However, central lines are substantially used also in non-ICU settings.³⁵ The first of two pilot studies at HUG, performed by Zingg and colleagues, revealed that more CVC-days accumulate in non-ICU units (62%) compared to the ICU (38%).³⁵ The study set the stage to prepare the later hospitalwide intervention study.⁴⁵ The distribution of CVC-days in non-ICU units and in the ICU was similar in the hospitalwide intervention study (62% vs. 38%, respectively), which was performed from 2008 to 2011.^{35,45} The study analysed 3952 patients with 6353 CVCs accumulating 61,366 catheter-days. In total, 106 patients had 114 CLABSIs with a cumulative incidence of 1.8 infections per 100 catheters. The multimodal and multidisciplinary prevention strategy as outlined above, significantly reduced the quarterly IDs after adjusting for various confounding factors (incidence rate ratios [95% confidence interval]: 0.92 [0.88–0.96]; $P<0.001$). The IDs in the first and last study year were 2.3/1000 catheter-days and 0.7/1000 hospital-wide, 1.7/1000 and 0.4/1000 in the ICUs, and 2.7/1000

and 0.9/1000 in non-ICU settings, respectively. Median time-to-infection was 15 days (Interquartile range, 8-22).

Both intervention projects by Zingg and colleagues in Zurich and at HUG are examples of successful multimodal prevention strategies.^{45,117} The projects promoted comprehensive best practice procedures and both used different modes and professions to provide education and training. While in Zurich, the project was planned in focus groups among IPC and nurses from the participating ICUs, at HUG the project was planned by an interdisciplinary team among IPC, anaesthesiology, and the board of nursing. Education was offered ex-cathedra and in hands-on workshops for nurses at bedside in Zurich. At HUG, doctors were trained in half-day practical simulation laboratory workshops. Nurses were trained in the wards by a train-the-trainer strategy and using a modular E-learning programme (www.carepractice.net).^{45,117} The latter was selected due to the expected large number of nurses to be trained (up to 1500).

Bundle strategies may not be transferrable directly to non-ICU settings, as generalizability of these interventions is not known.²⁷¹ However, the hospital-wide intervention at HUG used the same strategy for both ICU and non-ICU settings, with significant CLABSI reductions in ICU (1.7/1000 vs. 0.4/1000) and non-ICU settings (2.7/1000 and 0.9/1000).⁴⁵ Risks and prevention effects follow the same logic in the two settings with the exception that CVCs in the ICUs are much more often accessed in the ICU and may accumulate a similar number of accesses despite the shorter dwell-time as suggested by the study about CVC indications by Zingg and colleagues.³⁴

Education and training

“Team- and task-oriented education and training” and “Use of guidelines in combination with practical education and training” were two of the 10 key components identified in the above-mentioned systematic review on the organisation and management of IPC.⁹⁴ As a general

principle, education and training should be hands-on,²⁷² at the bedside¹¹⁷ and/or use skills' laboratories.^{45,244,273-277} Simulator-based training decreased CRBSI rates by 84% from 3.2 to 0.5/1000 CRBSI/1000 catheter-days ($P<0.001$) in a report by Barsuk and colleagues, and by 71% from 3.5/1000 to 1.0/1000 CRBSI/1000 in a study by Khouli and colleagues.^{273,274} Twelve months after simulation-based learning, 87.1% of residents still passed the skills' test.²⁷⁵ Multidisciplinary focus groups have been shown to be important in focusing IPC programmes on the target of interest and contributed to improved adherence to hand hygiene protocols and reduced HAI rates.²⁷⁸⁻²⁸⁰ Focus groups and collaboration in a multidisciplinary group were key in preparing successful CRBSI prevention programmes in Zurich and at HUG.^{45,117} Qualitative studies in hand hygiene showed that although formal training is effective,²⁸¹ individual experience is perceived to be more important for infection prevention.²⁸² In addition, strategies using traditional approaches based on logic and reasoning were perceived as less likely to be beneficial.^{94,283} Education and training programmes should be audited against predefined checklists revised over time to take into account local barriers and healthcare worker behaviour.⁹⁴ Similarly, knowledge tests and competency assessments help to detect gaps and to adjust education and training activities to local needs. Guidelines as stand-alone documents do not change practice as evidenced in a US study investigating whether an updated hand hygiene guideline was implemented in US hospitals or not.²⁸⁴ Although 90% of the contacted healthcare workers reported knowledge of the document, only 44% of the visited hospitals were evidenced to implement the guideline. "Knowledge" alone does not change behaviour. Doctors showed low adherence to MSB precautions for CVC insertion at a time when its effectiveness had been evidenced for more than 10 years and its use recommended by several national guidelines.^{122,235} Attitudes towards guidelines were more positive among nurses than doctors, and in paediatric than in adult ICUs.²⁸⁵ Guidelines are indispensable documents to set the stage for updating procedures, but they must be made "living" by being integrated in practical education and training.⁹⁴

Organisation and management of infection prevention and control

IPC is more than tackling CRBSI and, although CRBSI prevention can be perceived as an example of opportunities, possibilities, successes and limitations of IPC, its organisation and management is more complex. Initiated by the ECDC, a comprehensive systematic review was performed with the aim to identify the most effective and generally applicable elements of acute-care infection control and prevention programmes and to identify indicators of structure and process for monitoring: The systematic review and evidence-based guidance on organisation of hospital infection control programmes (SIGHT) project.⁹⁴ Based on almost 50,000 titles and abstracts, a final number of 92 studies of sufficient quality was selected to build the evidence base for key components in successful IPC. A panel of European experts (IPC, patients' safety, public health, quality improvement, health policy) was established to assess the rigour of the systematic review, and to score ease of implementation and EU-wide applicability of the key components. For each key component, process and outcome indicators were defined. A set of 10 key components with associated process and outcome indicators was identified and defined (Table 4).

Table 4: Ten key components and indicators of organisational maturity and structure for a successful implementation of infection prevention and control published by the European Centre for Disease Prevention and Control

Key component	Indicators
1 An effective infection-control programme in an acute care hospital must include as a minimum standard at least one full-time specifically trained infection-control nurse per up to 250 beds, a dedicated physician trained in infection control, microbiological support, and data management support ¹⁸⁸	Continuous review of surveillance and prevention programmes, outbreaks, and audits; infection control committee in place, inclusion of infection control on the hospital administration agenda, and defined goals; appropriate staffing and budget for infection control

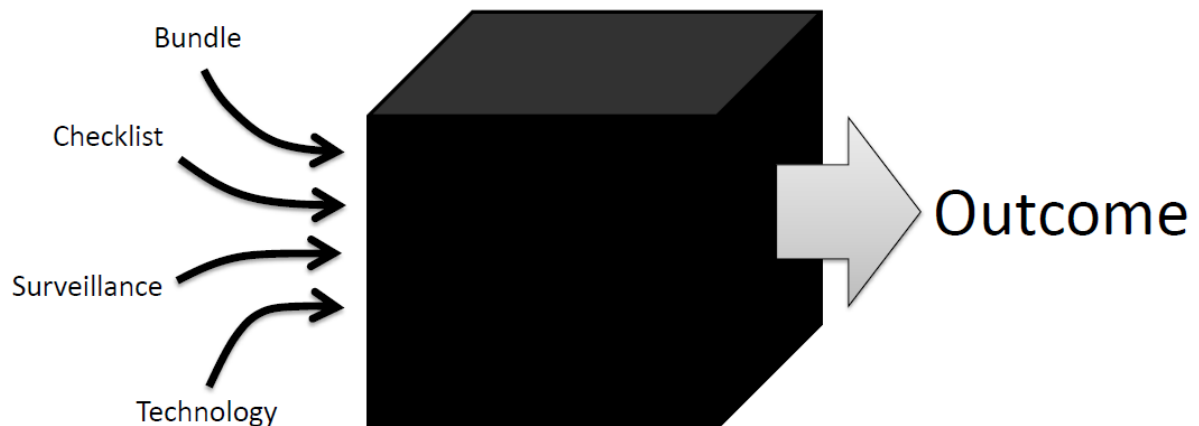
2	Ward occupancy must not exceed the capacity for which it is designed and staffed; staffing and workload of frontline staff must be adapted to acuity of care, and the number of pool or agency nurses and physicians used kept to a minimum ^{108-110,112,113,140,286-299}	Average bed occupancy at midnight, average numbers of frontline workers, and the average proportion of pool or agency professionals
3	Sufficient availability of and easy access to materials and equipment, and optimisation of ergonomics ^{262,300-308}	Availability of alcohol-based hand rub at the point of care and sinks stocked with soap and single-use towels
4	Use of guidelines in combination with practical education and training ^{284,285,300-303}	Adaptation of guidelines to local situation, number of new staff trained with the local guidelines, teaching programmes are based on local guidelines
5	Education and training involves frontline staff and is team and task oriented ^{116,272,274,278,279,281-283,285}	Education and training programmes should be audited and combined with knowledge and competency assessments
6	Organising audits as a standardised (scored) and systematic review of practice with timely feedback ^{242,312-315}	Measurement of the number of audits (overall, and stratified by departments, units and topics) for specified time periods
7	Participating in prospective surveillance and offering active feedback, preferably as part of a network ^{27,304-314}	Participation in national and international surveillance initiatives, number and type of wards with a surveillance, regular review of the feedback strategy
8	Implementing infection-control programmes following a multimodal strategy, including tools such as bundles and checklists developed by multidisciplinary teams, and taking into account local conditions ^{116,189,237,240,262-266,278,280,282,303,304,307,327-341}	Verification that programmes are multimodal; measurement of process indicators; measurement of outcome indicators
9	Identifying and engaging champions in the promotion of intervention strategies ^{264,265,315-317}	Interviews with frontline staff and infection-control professionals
10	A positive organisational culture by fostering working relationships and communication	Questionnaires about work satisfaction, crisis management, and human resource

This “ensemble” of the 10 key components can be perceived as the “multimodality of IPC” where the individual variables for success are each of the components. As will be explained below, implementation occurs in a local context of which IPC also is a context – a context within a context. IPC strategies such as CLABSI prevention programmes are not detached from determining factors such as organisation of IPC, staffing, infrastructure, and organisational culture. Surveillance, audits, feedback, education and training are actions on this background. The SIGHT project concluded that “IPC is a priority for patients’ safety, should involve healthcare workers at all levels, and be part of the hospital organisation as a whole. Staffing must be adequate to meet task requirements without leading to excessive workload. For prevention purposes, IPC programmes need to translate the key components into workable documents and programmes that take the local context into account. Programmes should be planned by multidisciplinary groups, take into account local guidelines, follow a multimodal intervention strategy that emphasises hands-on training, and be regularly assessed, and adjusted if necessary”.⁹⁴

Implementation of best practice procedures

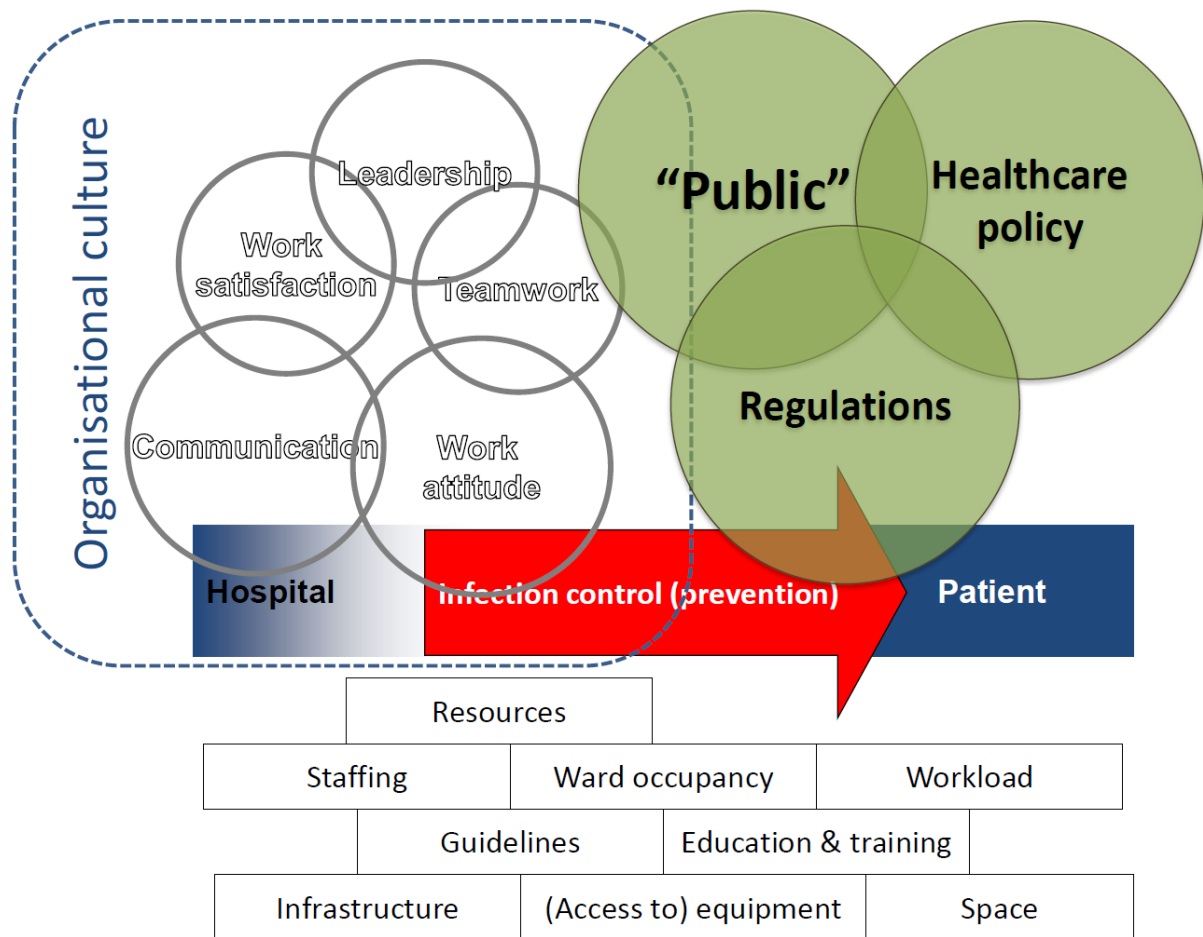
Studies on technology and practice change in the context of HAI prevention often report only the characteristics of the intervention, but rarely comment on implementation (Figure 9).

Figure 9: How publications report interventions.



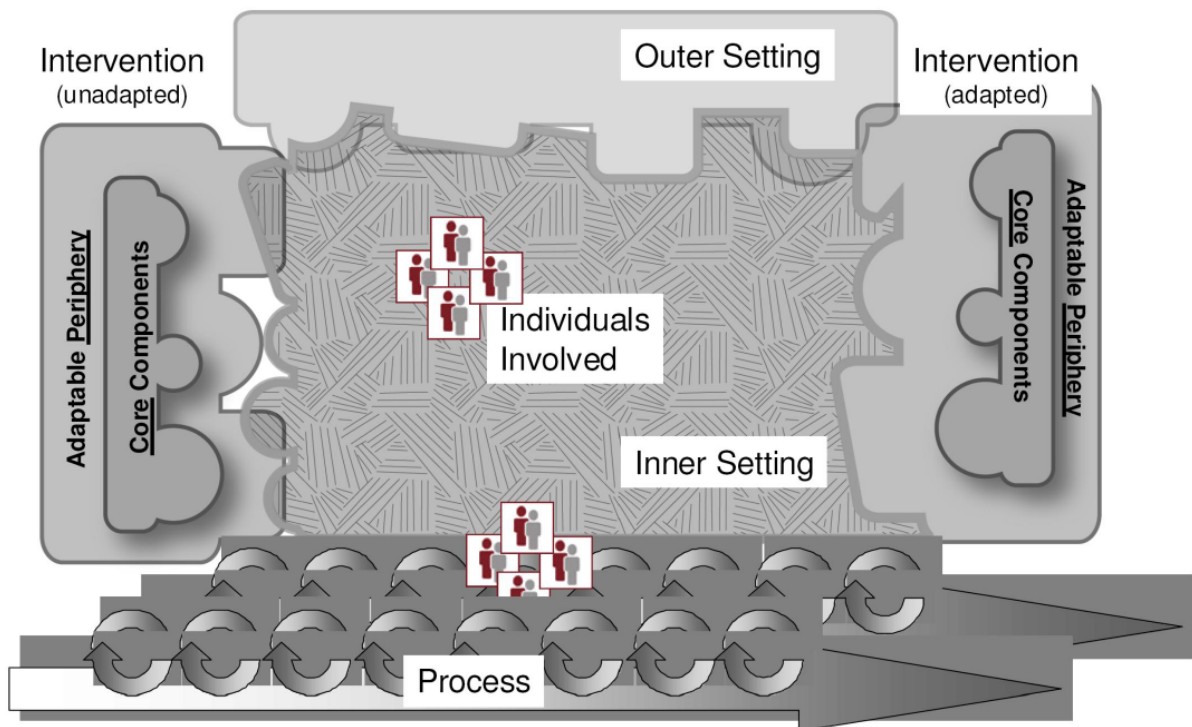
However, even the most effective evidence-based tool or prevention practice may not be applied if serious barriers prevent its implementation process. Hospitals often struggle to implement evidence-based recommendations.¹⁹⁰ IPC programmes aiming at changing the behaviour of healthcare workers depend on various aspects. The more tangible factors include infrastructure, resources, ward occupancy, staffing, and available documents. The less tangible factors include “organisational” culture, which is a concept including structure, work organisation, work satisfaction, and management. In addition, extra-hospital aspects interfere directly or indirectly with decision-making and prioritising projects in the hospital.³¹⁸ Involvement of key stakeholders in hospitals can lead to innovation adoption and implementation compatible with structural and cultural contexts.³¹⁹ The entity of tangible and non-tangible aspects in an organisation and the perception and beliefs of the stakeholders form a “context” in which implementation takes place (Figure 10).

Figure 10: Aspects of tangible and less-tangible factors forming the context in which implementation takes place.



Damschroder and colleagues developed a conceptual model named the Consolidated Framework of Implementation Research (CFIR).³²⁰ Five major domains interfering with successful implementation can be defined: intervention characteristics; outer setting; inner setting; characteristics of the individuals involved; and the process of implementation (Figure 11). The five dimensions of CFIR are not static; their contribution to implementation can only be understood by their interaction. No dimension is a stand-alone, but by interfering together they form a picture and a reality check when linked to what is observed in our institutions.

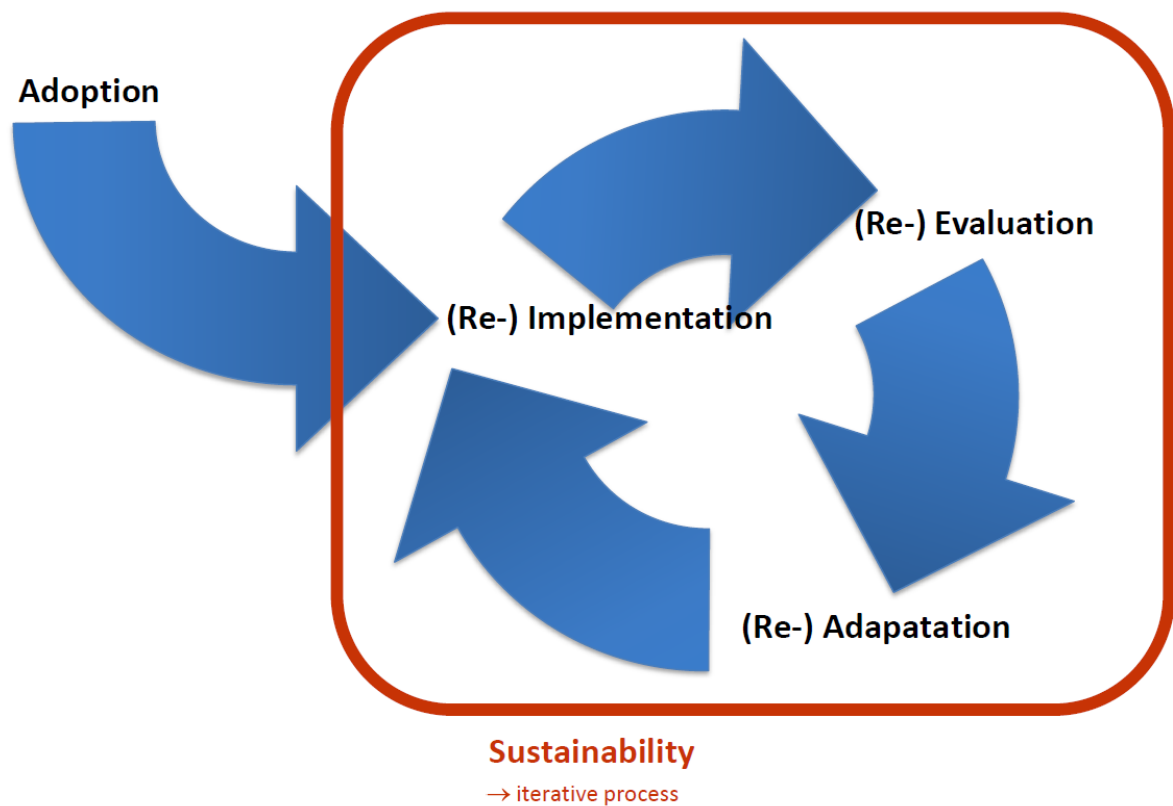
Figure 11: Major domains of the *Consolidated Framework of Implementation Research**



*With permission of the authors³²¹

Multimodality and multidisciplinary of projects improve the likelihood of implementation success because they take into account the fact that the different stakeholders are involved in the steps of planning and implementing the intervention. One of the key aspects of complying with the idea of multimodality and multidisciplinary is the active participation of stakeholders in training their peers.⁴⁵ Education and training in the successful hospital-wide CRBSI-prevention programme at HUG was executed by peers (anaesthesiologists trained anaesthesiologists and intensivists; nurses trained nurses).⁴⁵ Before, but also during the process, implementation barriers should be identified, prioritised, and removed.³²² Sustainability of a project can be perceived as an iterative process of implementation, evaluation, and adaptation (Figure 12).

Figure 12: Sustainability as an iterative process of implementation, evaluation, and adaptation



Setting the stage among stakeholders to pass the message of prevention was a successful strategy in the Michigan project.¹²⁴ The initiative was flanked by a strategy named the Comprehensive Unit-based Safety Program (CUSP).^{123,124} CUSP was originally intended to improve the safety culture, but facilitated adoption and implementation of the bundle strategy by strengthening leadership and inviting the hospital board to take an active part in the project.³²³ It helped to reframe CRBSI as a social problem.¹³ HAI prevention can only be successful if it is a priority, not only for the IPC professional or a champion in the unit, but at all hospital levels, including hospital management.³²⁴ Mistakes can be committed at any level, but networking among the different (CFIR-) dimensions and stakeholders can balance out shortcomings at other levels. Leaders are important in any organisation. Unfortunately this does not only work in the positive, but also in the negative sense. Inconsistency between the management's verbal and written commitments compared with its daily support is

negatively perceived by healthcare workers.¹¹⁴ Leaders of hospitals who were successful in HAI prevention cultivated a culture of clinical excellence and effectively communicated it to staff; focused on overcoming barriers dealing directly with resistant staff or process issues that impeded HAI prevention; inspired their employees; and thought strategically while acting locally.¹¹⁵ Middle managers are more likely to support implementation if they believe that doing so will promote their own organisational goals and if they feel involved in discussions about the implementation.³²⁵

DISCUSSION AND PERSPECTIVES

The studies conducted by the candidate and summarized here well demonstrate the prerequisites for the conduct and success of multimodal and multidisciplinary intervention studies in CRBSI or CLABSI prevention. The first study exemplifies the importance of surveillance to produce meaningful data.⁷ HAI incidence surveillance is costly, particularly when performed hospital-wide. For study purposes, incidence data can be produced, but hospitals have little resources available for the prospective surveillance of individual patient-based data.⁷ Instead, they focus on areas of increased risk such as ICUs, NICUs, surgery or oncology and/or organise prevalence surveys to obtain a broad snapshot of HAI in the entire hospital. The Geneva study exploring the advantages and disadvantages of point and period prevalence surveys discovered that the period methodology is more suitable for HAI surveillance in long-term care facilities, while the simpler point prevalence survey methodology is sufficient for acute care facilities. On the limitation side, prevalence surveys were found to be lacking in sufficient power to detect HAI differences from year to year, unless they are massive. The results of the successful Geneva hospital-wide CLABSI prevention programme⁴⁵ was not reflected in the findings of the yearly prevalence surveys. However, the achieved CLABSI reduction was mirrored in our prospective all-cause BSI surveillance based on electronic case-finding combined with patient chart assessment.⁴⁶

The success of the hospital-wide CLABSI prevention project at HUG is the result of its multimodal and multidisciplinary character. The programme was comprehensive by addressing both CVC insertion and care and by preventing CRBSI hospital-wide.⁴⁵ This comprehensiveness required the commitment of multiple professions from various disciplines. One of two pilot studies provided important data for subsequent study planning.³⁵ The results suggested that CRBSI rates in non-ICU settings are similar to the ICU and that CRBSI rates may be particularly high in abdominal surgery. Although more CVCs were used in the ICU (resulting in a much higher utilisation ratio), the cumulative number of catheter-days was higher outside the ICU. The magnitude of this proportion (60%) was not expected

and has not been previously highlighted in the published literature. A second pilot study addressed healthcare workers' knowledge on the number and reasons for CVC use, the magnitude of unnecessary CVC-days, and if healthcare workers were always aware of the reason why a CVC was in place.³⁴ Treatment with intravenous antibiotics was the main indication for CVC use both in the ICU and in non-ICU units. However, this was the only similarity of CVC use between ICU and non-ICU units. CVCs in the ICU were accessed for more indications at the same time, but the catheters were in place for only 4 days. CVCs in non-ICU units were accessed for fewer indications, but catheters were in place for 8 days. Given the similar CLABSI IDs in ICU and non-ICU units, we assumed that the most important risk for CRBSI is the number of accesses to the CVC (several per day in the ICU [shorter dwell-time]; less per day in non-ICU units [longer dwell-time]). Our study could not formally prove this hypothesis and, to our knowledge, no other study has formally confirmed this relation. Data obtained by the two pilot studies influenced the planning of the intervention study,⁴⁵ particularly the content of education and training.^{34,35}

The study group of the hospital-wide Geneva CLABSI prevention study included doctors and nurses from IPC, anaesthesiology, and the nursing department.⁴⁵ Similar to the Zurich experience, the study protocol was developed in a multidisciplinary manner and the education and training contents were discussed with the frontline stakeholders before becoming active. The hospital-wide concept challenged the organisation of education and training both on the design level and on the knowledge and capacity delivery levels. Given the difference in the expected numbers of doctors and nurses to be trained, the design and implementation of education and training was adapted. The study team prepared simulation training for doctors in a skills' laboratory and developed a modular E-learning training (www.carepractice.net) for nurses. One of the key aspects in the implementation process was the fact that healthcare professionals were trained by their peers (anaesthesiologists by anaesthesiologists; nurses by nurses). The success of this strategy was to such an extent that frontline healthcare workers perceived the project being initiated by their own service.

IPC almost completely disappeared in the perception of the stakeholders and trained healthcare workers, which was an intended effect to allow them to identify with the project. To avoid any perception of complexity of the intervention by the frontline nurses, it was broken down into 4 modules in the Zurich study and 5 modules in the Geneva study. The concept of breaking down complex interventions to palatable pieces is a known positive determinant in implementation research.^{320,326}

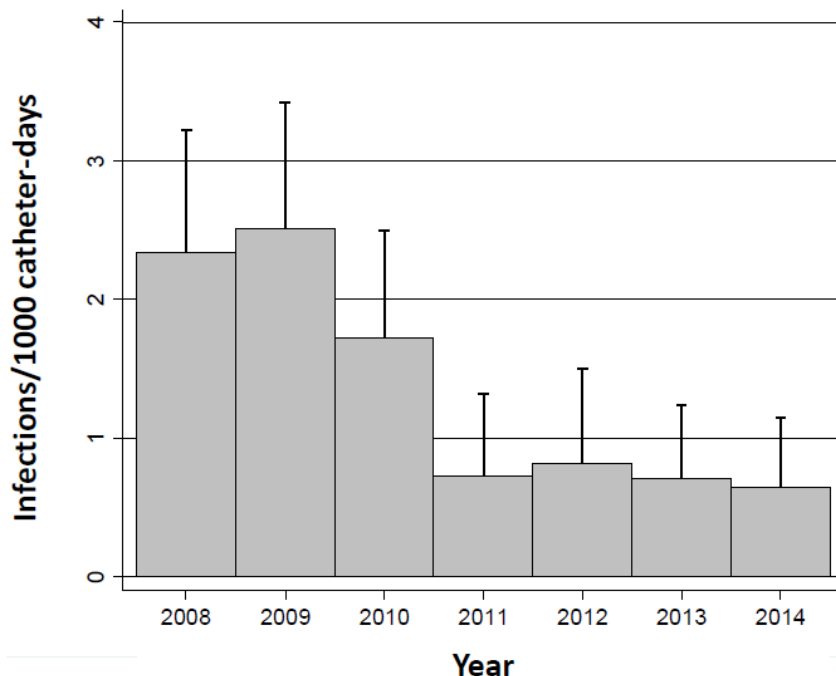
Successful implementation of a strategy aiming at behavioural change takes into account the identification of barriers, ideally already before the intervention starts but also – and even more importantly – during the implementation process.^{320,322,327} Barriers can be best identified by using qualitative research. Saint and colleagues published the combined quantitative and qualitative results of a national catheter-associated UTI prevention initiative in the USA.^{328,329} The qualitative part provided information to understand why some hospitals may have failed to implement a programme called “bladder bundle”. Dixon-Woods and colleagues performed an ex-post-theory about the Michigan project.¹³ The idea of doing this was partially based on the experience with the English “Matching Michigan” project, which aimed to repeat the success of the Michigan project in a different context.²⁷⁰ Overall, CLABSI rates significantly decreased, but not in direct association with the introduction of the bundle.²⁷⁰ In a following paper explaining this “failure”, the authors concluded that “improved implementation of procedural good practice may occur through many different routes, of which programme participation is only one”.³³⁰ This is a good explanation why multimodal interventions work. “Multimodal” does not just refer to a bundle of procedural actions. It must be perceived as a universal strategy addressing procedures comprehensively and by using various modes to transmit the message with the aim to encourage healthcare workers to change their behaviour. On the “receptive” side we cannot predict, which mode or part of the multimodal intervention is effective. Multimodality acts in a way like a shotgun where we cannot say which bullets hit the target. In quality improvement initiatives we work with individuals and professionals who have their own perceptions, beliefs, cultural backgrounds, and their

individual ways of coping.³³¹ In the European PROHIBIT project, we combined quantitative with qualitative research in a multicentre CRBSI prevention initiative among ICUs from different European countries.³³² Similar to the findings of the English “Matching Michigan” project,^{270,330} we also found that a CRBSI decrease is measurable and significant, but that it is not always timely to the start of the behavioural change intervention (*manuscripts in preparation*).

CRBSI initiatives must be adapted not only based on identified barriers, but new aspects may make adjustments necessary. One such aspect was the introduction of ultrasound in CVC insertion in our hospital. Between 2008 and 2011, the use of ultrasound significantly increased from 9.6% to 55.8%.^{231,232} The introduction of this device at HUG necessitated adjustments of the workshops as maintaining an aseptic technique during CVC insertion while handling ultrasound is more complicated. The concurrence of introducing ultrasound with our intervention study allowed to investigate the question if ultrasound prevents or promotes CRBSI.^{231,232} In contrast to previous publications in the field,²³⁰ we did not observe a significant influence of ultrasound on CRBSI in a positive or in a negative manner. Following a letter³³³ published in a peer-reviewed journal, which challenged our findings, we revisited our data and tested for variables, such as multiple punctures and experience of staff. The results did strengthen our original findings.²³² At HUG, the use of ultrasound for CVC insertion has become standard practice in anaesthesiology and intensive care where 90% of all institutional CVCs are inserted, including those for PN, haemodialysis, and chemotherapy.²³² We adapted our multimodal strategy to the introduction of this device and all doctors in anaesthesiology and intensive care are trained accordingly.

At HUG, the simulation workshops for doctors continued after the published period of 2008-2011. Yearly post-study CLABSI surveillance (2012-2014) has demonstrated the sustainability of low CLABSI rates (Figure 13).

Figure 13: Yearly incidence densities of central line-associated bloodstream infections – hospital-wide multidisciplinary and multimodal prevention programme at the University of Geneva Hospitals, 2008-2014.



A new aspect in CRBSI prevention is optimal nutritional energy provision. The first of the two mentioned papers on this subject was performed in the ICUs at HUG and the University Hospital of Lausanne.^{106,139} SPN to provide optimal energy intake for 5 days after 4 days of enteral feeding significantly reduced HAI. From an IPC perspective, PN was always considered a risk for CRBSI and we assumed that SPN may be a risk for overall HAI and CRBSI in particular even in the SPN study. Indeed, during the first SPN days there was no difference in HAI or in CRBSI. However, patients receiving SPN had fewer HAIs after the intervention period. Other studies and a meta-analysis have shown that patients receiving enteral nutrition are less likely to get HAI.^{131,334} Thus, there is controversy in the field.¹³⁹ Clearly, it is difficult to directly compare the studies because the methodologies of nutrition provision were different.^{106,334} However, there is evidence that the risk of malnutrition-related infection is real. A placebo-controlled study among malnourished children in Malawi showed that adding antibiotics to therapeutic regimens for uncomplicated severe acute malnutrition

reduced mortality (OR [95% CI]: 1.66 [1.22–2.27]; $P=0.002$).³³⁵ Malnourished children are known to have compromised mucosal defences (both respiratory and intestinal).^{336,337} Studies of bacteraemia in malnourished children suggest that most severe invasive bacterial infections are due to translocation across such compromised mucosal surfaces.^{335,338} An *in vitro* study showed that low protein feeding in lymphocytic choriomeningitis virus immune mice resulted in a two-fold decrease in lymphocytic choriomeningitis virus-specific CD8 memory T-cells and that those memory cells were markedly less responsive to acute proliferative signals.³³⁹ A meta-analysis showed that immunomodulating diets decreased infections in ICU patients (OR [95% CI]: 0.63 [0.47–0.86]; $P=0.004$).³⁴⁰ When supplemented with fish oil, such products even had a positive effect on mortality (OR [95% CI]: 0.42 [0.26–0.68]) and reduced hospital length of stay by 6.28 days (95% CI: 2.6–9.9).³⁴⁰ The anti-inflammatory effects of fish oil^{341–343} and the reduction of sepsis and UTI by adding glutamine^{344–346} have been shown repeatedly. This supports the idea of a preventive effect of nutrition on HAI, particularly in the elderly where we would expect the biggest challenge of malnutrition in high-income countries. In a very recent prevalence survey, we tested this hypothesis hospital-wide at HUG.¹⁰⁷ Measured energy intake $\leq 70\%$ of predicted energy needs was associated with HAI. This finding further supports the idea that insufficient dietary intake may be a risk for HAI (without excluding reverse causality). This is a new area of HAI prevention and in the future we may take this into consideration and include nutritionists in multidisciplinary prevention activities.

Children, infants and neonates in PICUs and NICUs are particularly at risk for HAI.^{347,348} We summarised 8 years of surveillance in the NICU at HUG.⁸² The surveillance illustrates that the rates of CRBSI in this population is very different from adults as is the type of central lines (umbilical catheters). An unexpected finding was that there was no difference between umbilical lines and PICC lines in dwell-time as a risk for CRBSI. Five studies specifically addressed dwell-time as a risk factor for CLABSI in neonates.^{82,348–352} Although a first study by Milstone and colleagues suggested progressive risk increase over time,^{349,350} a

subsequent large multicentre study identified risk increase only in the first 14 days with a risk remaining at a constant level thereafter. A similar trend was reported in the HUG study in which the dynamics between umbilical and PICC lines were similar.^{82,348} Compared to adults where many CLABSI prevention studies have been reported in varied settings using a range of bundles and multimodal interventions,^{94,190} the number of multimodal prevention studies in the NICU^{242,353,354} and PICU^{258,269,355} is rather low and the major challenge remains the implementation of practices related to behavioural change.^{348,356}

CONCLUSION

The prevention of CRBSI is the paradigm of IPC. Successful strategies need sound data from surveillance. In the past, CRBSI interventions included technology, but behavioural change interventions addressing best practice have become more prominent. In addition, the latter have been far more successful than the simple introduction of a technical device. Behavioural change interventions to achieve best practice are not easy and such programmes must follow a multimodal strategy developed by multidisciplinary teams, and taking into account local conditions. Multimodal strategies include bundles or more comprehensive procedures, which are a combination of technology and best practice. These are delivered by different “modes” such as lectures, visual reminders, simulation training, bedside teaching, knowledge tests, or any other original and imaginable idea to help change the addressed stakeholders’ behaviour. The preparation and implementation of multidisciplinary strategies must include stakeholders from different disciplines and professions and education and training must involve frontline staff. If possible, teaching and training should be delivered by peers. The delivered information should be rooted in evidence and based on widely accepted guidelines. Newly discovered areas in HAI prevention, such as optimized nutritional energy intake, must be taken into account as part of multimodal and multidisciplinary prevention strategies. The major challenge for HAI prevention is “implementation” and more research must be invested on this aspect in the future in order to provide hospitals with manageable information about how to conduct effective multimodal strategies in daily practice.

ABBREVIATIONS IN THE DOCUMENT

ABHR	Alcohol-based handrub
BSI	Bloodstream infection/s
CABSI	Catheter-associated bloodstream infection
CAUTI	Catheter-associated urinary tract infections
CDC	US Centers for Disease Control and Prevention
CFU	Colony-forming units
CHG	Chlorhexidine gluconate
CHG/SS	Chlorhexidine-silver sulfadiazine
95% CI	95% confidence interval
CFIR	Comprehensive Framework of Implementation Research
CLABICS	Central line-associated bloodstream infections and clinical sepsis
CLABSI	Central line-associated bloodstream infection/s
CoNS	Coagulase negative Staphylococci
CRBSI	Catheter-related bloodstream infection/s
CSS	Cross-sectional study
CVC	Central venous catheter
EARSS	European Antibiotic Resistance Surveillance System
EARS-Net	ECDC European Antibiotic Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EPIC	Evidence-based Practice in Infection Control
EPINE	Estudio de Prevalencia de las Infecciones Nosocomiales en España
ESAC	European Surveillance of Antibiotic Consumption
ESAC-Net	ECDC European Surveillance of Antibiotic Consumption Network
EU	European Union
HABSI	Healthcare-associated bloodstream infection
HAI	Healthcare-associated infection/s
HAI-Net	ECDC Healthcare-Associated Infection Network
HAP	Hospital-associated pneumonia
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HICPAC	Healthcare Infection Control Practices Advisory Committee
HR	Hazard ratio
HUG	University of Geneva Hospitals
ICU	Intensive care unit
ID	Incidence density
IDSA	Infectious Disease Society of America
INICC	International Infection Control Consortium
IPC	Infection prevention and control
IPSE	Improving Patient Safety in Europe
KISS	Krankenhaus Infektions Surveillance System
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSB	Maximal sterile barrier
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
NCC	Non-controlled cohort study
NHSN	National Healthcare Safety Network
NICU	Neonatal intensive care unit
NNIS	National Nosocomial Infection Surveillance
OR	Odds ratio
PICC	Peripherally inserted central catheter
PICU	Paediatric intensive care unit
PN	Parenteral nutrition
PPS	Point prevalence study
PROHIBIT	Prevention of hospital infection by intervention and training

PVC	Peripheral venous catheter
QRS	Qualitative research study
RCT	Randomised controlled trial
RR	Relative risk
SENIC	Study on the Efficacy of Nosocomial Infection Control
SIGHT	Systematic review and evidence-based guidance on organization of hospital infection control programmes
SPN	Supplemental parenteral nutrition
SSI	Surgical site infections
TNA	Total nutrient admixtures
TPN	Total parenteral nutrition
UTI	Urinary tract infections
VAP	Ventilator-associated pneumonia
VLBW	Very-low-birth-weight
WHO	World Health Organization

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APPENDICES

- **Appendix 1:** Monitoring healthcare-associated infections by period vs point prevalence – what is the difference. **Zingg W**, Huttner B, Sax H, Pittet D. *Infect Control Hosp Epidemiol* 2014;35:674-684 (Impact factor: 3.0; Citations: 1)
- **Appendix 2:** Impact of a prevention strategy targeting hand hygiene and catheter care on the incidence of catheter-related bloodstream infection. **Zingg W**, Imhof A, Maggiorini M, Stocker R, Keller E, Ruef C. *Crit Care Med.* 2009;37:2167-2173 (Impact factor: 6.7; Citations: 52)
- **Appendix 3:** Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. **Zingg W**, Sax H, Inan C, Cartier V, Diby M, Clergue F, Pittet D, Walder B. *J Hosp Infect.* 2009;73:41-46 (Impact factor: 3.0; Citations: 35)
- **Appendix 4:** Hospital-wide survey of the use of central venous catheters. **Zingg W**, Sandoz L, Inan C, Cartier V, Clergue F, Pittet D, Walder B. *J Hosp Infect.* 2011;77:304-308 (Impact factor: 3.0; Citations: 14)
- **Appendix 5:** Hospital-wide multidisciplinary and multimodal intervention program to reduce central venous catheter-related bloodstream infections. **Zingg W**, Cartier V, Inan C, Touveneau S, Theriault M, Pittet D, Walder B. *PLOS One* 2014;9:e93898 (Impact factor: 4.2; Citations: 3)
- **Appendix 6:** Hospital organization, management and structure in the context of healthcare associated infection prevention - a systematic review. **Zingg W**, Holmes A, Dettenkofer M, Clack L, Secchi F, Goetting T, Magiorakos A, Pittet D, and the SIGHT-study group. *Lancet Infect Dis.* 2015; 15: 212-224 (Impact factor: 19.7; Citations: 2)
- **Appendix 7:** No association between ultrasound-guided insertion technique and bloodstream infections in central venous catheters – a prospective observational study. Cartier V, Haenny A, Inan C, Walder B, **Zingg W**. *J Hosp Infect* 2014;87:103-108 (Impact factor: 3.0; Citations: 2)

- **Appendix 8:** Optimization of energy provision with supplemental parenteral nutrition improves the clinical outcome of critical ill patients: a randomized controlled clinical trial. Heidegger CP, Berger MM, Graf S, **Zingg W**, Darmon P, Thibault R, Pichard C. *Lancet*. 2013;381:385-393 (Impact factor: 38; Citations: 111)
- **Appendix 9:** Healthcare-associated infections are associated with insufficient dietary intake: an observational cross-sectional study. Thibault R, Makhoul AM, Kossovsky MP, Iavindrasana J, Chickhi M, Meyer R, Pittet D, **Zingg W**, Pichard C. *PLOS One* 2015; 10: e0123695 (Impact factor: 4.2; Citations: 0)
- **Appendix 10:** Individualized catheter surveillance among neonates: a prospective 8-year single center experience. **Zingg W**, Posfay-Barbe K, Pfister R, Touveneau S, Pittet D. *Infect Control Hosp Epidemiol*. 2011;32:42-49 (Impact factor: 3.0; Citations: 7)