Universitat Internacional de Catalunya

Tesis doctoral

The epidemiology of catheter-related bloodstream infections in a tertiary care center: Prevention and mortality

Patrick Saliba

The epidemiology of catheter-related bloodstream infections in a tertiary care center: Prevention and mortality

Patrick Saliba

Dissertation for degree Philosophiae Doctor (PhD) at Universitat Internacional de Catalunya,

Barcelona,Spain.2018

Directors: Dr. Miquel Pujol and Dr. Jose M. Martínez-Sánchez

Tutor: Dr. Xavier Corbella

uic barcelona

Dedicated to all the people that have been involved in the accomplishment of this doctoral thesis and all who have been by my side during this adventure, especially my family

“If you have faith and do not doubt, not only will you do what was done to the fig tree, but even if you say to this mountain, 'Be lifted up and thrown into the sea,' it will happen” **Matthew 21:21**

Research environment

The research leading up to the thesis here presented started end of 2015. Collaborators of this PhD were affiliated with:

- Department of Infectious Diseases, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.

- Department of Microbiology, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.

- Department of Medicine, Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya, Josep Trueta s/n, 08195 Sant Cugat del Vallès, Barcelona, Spain.

Table of contents

Acknowledgements

Acknowledgements

First of all I would like to thank GOD for all of his blessings and for the power he gave me to accomplish this long journey of research work. I would like to thank him for the beautiful family I have, for my parents, who allowed me to realize my dreams and move to Spain to study and evolve and make a success story.

I owe gratitude to the director of my doctoral thesis Dr. Miquel Pujol, for believing in my potentials, directing my thesis project, providing me with a lot of scientific knowledge, training me on scientific research work, opening for me many doors for internships on clinical and research levels and helping me in the whole process of publication of scientific articles and to participate in Projects and congresses on European level.

I would like thank the tutor of my doctoral thesis Dr. Xavier Corbella, who has been my first support since the beginning of my academic journey in Barcelona. Not only directing my master thesis final work at the UIC but introducing me to the research team for prevention and infection control at Bellvitge University Hospital and tutoring the work of this doctoral thesis project.

Another moral and academic support for me was the Co-director of my doctoral thesis project Dr. Jose Maria Martinez. I am thankful for him sharing with me his knowledge in the public health field and statistics, supporting me throughout the articles ‘publication process and data analysis and for his continuous care and moral support to evolve and work hard.

To the infection control team at Bellvitge hospital, I own them gratitude for providing me with all the data and the resources that I needed to perform my work and for their collaboration in a healthy and friendly atmosphere of work and study.

I am thankful to the VINCat program and to Dr. Enric Limón for giving me a one life chance to be a part of the VINCat program and work with them as a center coordinator, researcher and contributor in the development of a protocol for prevention of catheter related bacteremia on a Catalan national level.

My experience in Spain would not have been as enriching and entertaining without my friends and my colleagues, so big thanks for all of them.

To all of you,

Gracias, Gràcies, Thank you, شكرا

Abbreviations

Abbreviations

PVC: Peripheral vascular catheter

CVC: Central vascular catheter

PICC: Peripheral inserted central catheter

HCAIs: Healthcare associated infections

CRBSI: Catheter related bloodstream infection

CRB: Catheter related bacteremia

PVCR-BSI: peripheral venous catheter related bloodstream infection

SAB: *Staphylococcus aureus* associated bacteremia

ICU: Intensive care unit

BUH: Bellvitge University Hospital

VINCat: Vigilància de les infeccions nosocomials de Catalunya

Summary

Summary

The present PhD thesis is a compedium of two publications broadening the knowledge on Catheter Related Bloodstream Infections (CRBSIs) outside intensive care units (ICUs), based on data collected from 2003 to 2016 from "Bellvitge University hospital" (BHU), in Barcelona,Spain. Catheter-related bloodstream infection (CRBSI) is a preventable cause of death, a common cause of nosocomial bacteremia and an increasing safety problem in hospitalized patients. In the last decade, the infection control unit in BHU has implanted a prevention program for CRBSIs. Herein, we examine the efficiency of the applied prevention program in reducing the rates of CRBSIs between 2003 and 2016 and we assess the risk factors for mortality associated with these CRBSIs.

Based on the results published in the first article , it can be observed that following the application of a prevention model for CRBSIs, the rates of peripheral CRBSI decreased significantly from 30 cases (1.17 episodes /10000 days) in 2003 to 8 cases in 2016 (0.34 episodes/10000 days of stay) and the rates of *Staphylococus aureus* (S.*aureus*) too, as the most associated microorganism with CRBSI from related infections, dropping from 18 episodes in 2003 (0.70 ep/10,000 pt-days) to 3 episodes in 2016 (0.14ep/10,000 pt-day) ($p<0.002$), as well as a decrease in mortality rates from 7 cases in 2003 (0.27ep/10,000 pt days) to 0 in 2016 (0.00ep/10,000 pt days in 2016 ($p<0.05$). Whereas in the second article, and after the analysis of all the data and cases of CRBSIs within the study period, *S.aureus*, a Charlson score of comorbidity >4 and Candida infections were proved to be major risk factors associated with mortality among patients with CRBSIs.

Taking everything together, the results obtained lead to the conclusion that although CRBSIs are a major threat to the patients' safety during hospitalization, yet, the application of an efficient preventive program such as the one applied in "BUH" was able to lead to a significant drop in the rates of CRBSIs and the associated mortality throughout the years. Moreover, we can conclude that *S.aureus* among other risk factors is a major threat to patients' safety, and a major risk factor associated with mortality, for which, broader preventive measures should be applied and enhanced appropriate treatments should be given to decrease the rates of S.*aureus* infections and its resistance forms.

List of articles

List of articles

The present doctoral thesis is composed of two scientific articles, both published in the Journal of hospital infection (Impact factor 3.354).The results of these articles were presented in various conferences and international congresses. The articles included in this thesis are the following ones, referred in the text by their Roman numerals:

Article I

Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, Berbel D, Martos P, Manuel Verge J, Tebe C, María Martínez-Sánchez J, Shaw E, Gavaldà L, Carratalà J, Pujol M.

Interventions to decrease short-term peripheral venous catheter-related bloodstream infections. Impact on incidence and mortality. J Hosp Infect. 2018 Jun 18. pii: S0195-6701(18)30324-4. doi: 10.1016/j.jhin.2018.06.010. [Epub ahead of print] PubMed PMID: 29928942.

Article II

Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, García D, Tubau F, Martínez-Sánchez JM, Carratalà J, Pujol M.

Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study. J Hosp Infect. 2018 May;99(1):48-54. doi: 10.1016/j.jhin.2017.11.002. Epub 2017 Nov 8. PubMed PMID: 29128346.

Scientific work

Scientific work

The work to achieve this research project was intensive ,multi-disciplinary and challenging. I was involved in collecting some data, conducting the analysis, perform the statistical work, write the articles and publishing them.Apart from the intensive work on the two published articles for this PhD project, I have been involved in various local and European research projects in the HCAIs prevention field. The involvement in these projects, validated my work for my doctoral studies related to CRBSIs and expanded my knowledege in various types of HCAIs such as the urinary catheter-related infections, the multi-resistant drugs orgranisms,the *Clostridium difficile* infections and surgical site infections.In addition, through the research period, I had the chance to attend and participate in two major congresses through posters exhibition and talks. Listed below are all the articles, congresses, research projects and studies that I took part of during the last three years of research work.

- **The impact of pre-filled saline flush syringes in reducing the incidence of peripheral venous catheter failure. A quasi-experimental study -Annex III (WoCoVA, 2018:** The 5th World congress on vascular access: 20-22 June 2018, Copenhagen, Denmark)

- **Anti-Superbugs: a European multicentral project to invent and propose a prototype to be implemented in hospitals for the detection of the MDROs (multidrug-resistant organism) -Annex VII**

- **Identification of biomarkers based on energy metabolism and oxidative stress in patients with urinary catheter-associated infections and development of biosensors for their determination in primary and hospital care**. Fundació Institut d'Investigació Sanitària Pere Virgili CENTRE: Hospital Universitari de Sant Joan -Project: [569/U/2018}-:Applied to La Marato de TV3

- **Incidence and risk factors for recurrent C. difficile infection in Catalonia, Spain- Merck Investigator Studies Program**

- **Study of the risk factors and prognostic factors of poor evolution and the impact on patients who have undergone a new episode of Clostridium difficile during the 2011-2017 period**

Background

Background

Reflexion as a PhD candidate

PhD or *Phylosophiae* Doctor does not refer solely to the field of philosophy, but is used in a broader sense in accordance with its original Greek meaning, which is "Love of wisdom" (Wikipedia.org).

Doing a PhD implicates and has to implicate a broad sense overpassing the threshold of science. It comes, as the original name says, to a higher philosophical level, a lover of wisdom. It refers to any kind of wisdom, scientific and personal wisdom. It implicates another way of thinking, to interact with your environment, with the people that surround you.

Healthcare associated infections

According to the World Health Organization "WHO", Health care-associated infection (HCAI), also referred to as "nosocomial" or "hospital" infection, is an infection occurring in hospitalized patients which was not present at the time of admission. HCAI can affect patients in any type of setting where they receive care and can also appear within 48-72 hours after discharge. HCAIs include occupational infections among working staff. Based on data from various countries, it can be estimated that each year, hundreds of millions of patients around the world are affected by HCAI. The burden of HCAI is several folds higher in low- and middle-income countries than in high-income ones.

Every day, HCAI results in prolonged hospital stays, long-term disability, and increased resistance of microorganisms to antimicrobials, massive additional costs for health systems, negative quality of care effect for patients and their family, and unnecessary deaths.

Although HCAI is the most frequent adverse event in health care, its true global burden remains unknown because of the difficulty in gathering reliable data: most countries lack surveillance systems for HCAI, and those that do have them

struggle with the complexity and the lack of uniformity of criteria for diagnosing it.

Catheter related bloodstream infections

Pathogenesis

Catheter-related bloodstream infections (CRBSI) are defined as the presence of bacteremia originating from an intravenous catheter[1]. It is one of the most frequent, lethal, and costly complications of venous catheterization and one of the most common causes of HCAIs. The intravascular catheters are integral to the modern practices and are inserted in critically-ill patients for the administration of fluids, blood products, medication, nutritional solutions, and for hemodynamic monitoring[1].

The contamination of the inserted catheter can be due to four recognized routes: 1-the *extra-luminal surface*, mostly colonized through the contamination at the skin insertion site; 2-the *intraluminal surface*, which is contaminated through catheters hubs and lines contamination by manipulations of the device by patients and/or healthcare worker; 3-by *insertion of contaminated drugs or infuses* ; 4-by *hematogenous colonization* from a distant site of infection[2]. This variety of sources (figure 1) should be taken into account in the methods used to diagnose an infection.

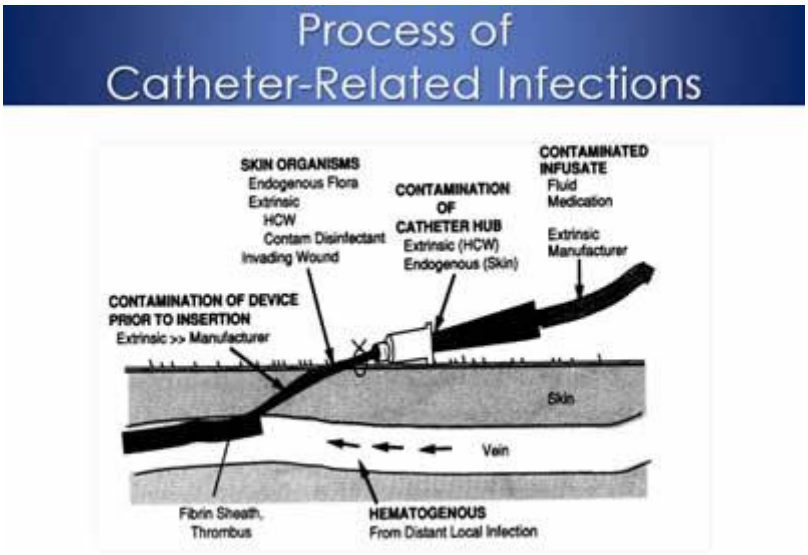


Figure 1: There are the main areas from which catheter related infections can originate. Infection can occur hematogenously, from a distant local infection. Contamination of the catheter device prior to insertion, skin organisms, or contamination of the catheter hub can all cause infection. Contaminated infusate can also cause infection.

The risk of a vascular catheter infection depends on the type of catheter, the insertion technique, the site of insertion, the sterility of the insertion procedure, the purpose of catheter use, site care, number of manipulations and specific host factors.[3] The catheter itself is the most significant extrinsic factor implicated in CRBSI.

Other than the type of catheter and catheter location, the most important extrinsic risk factors associated with the development of CRBSI include: duration of catheterization, catheter material, insertion conditions, skill of the catheter inserter and catheter-site care, some of the host factors (age, immunity status..) and finally the type of microorganism involved[3].

Infections and etiology

Microorganisms such as Staphylococci family, Enterococci, Aerobic Gram-negative bacilli and yeast can cause a CRBSI. However, Coagulase-negative staphylococci are considered to be the most common cause of CRBSIs. Severe forms of sepsis with a poor outcome are rare. Isolated fever or fever with inflammation at the catheter exit-site is common clinical manifestations. These infections may resolve with removal of the catheter only without further antibiotic therapy, although many experts suggest that antibiotics should be administered for a limited period of time[4].

On the other hand, among all the staphylococci family, *S.aureus* is considered to be the most common, and related Catheter infections may manifest as devastating metastatic infections and the risk of infective endocarditis is higher than for other microorganisms[5].

Prevention and mortality among patients with CRBSI

Preventive methods

Significant efforts have been made at different healthcare levels in order to reduce the incidence of CRBSI, mostly in intensive care units. Most of these initiatives have focused on preventive aspects, as evidence has shown that educational programs, simulation programs in addition to improving technical skills

in catheter insertion, allow the resident and physician to easily comply with guidelines and checklists[6]. The catheter insertion conditions are critical for the development of infections derived from the device. The current recommendations for the insertion of CVCs include the use of long sleeve gown, surgical cap, face mask, sterile gloves and large sterile sheets that completely cover the patient. Hand hygiene should be the standard practice, but compliance by health care professionals is still poor. Chlorhexidine, for example, has shown a better antiseptic performance as compared to regular Povidone iodine solutions[7].

While catheter removal is a mainstay of treatment in most of the cases, empiric antibiotic treatment is a common practice when dealing with CRBSIs. The choice of the antimicrobial agent depends on the severity of the systemic illness, the comorbidities, the most likely microorganisms and the local resistance profile[8].

CRBSIs in numbers

In spite of the various preventive measures applied to reduce the rates of CRBSI worldwide, the incidence of CRBSI reported is still significant and it varies from country to country and even hospital to hospitals.

Up until recently, over 250 000 CRBSIs occurred every year in the United States and over 80 000 of these appeared in ICUs.[7] These infections are associated with increased length of hospital stay from 10 to 20 days and increases in the cost of care from $4000 to $56 000[9].

According to a European study carried out in France, Germany, Italy and the UK[10], CRBSI accounted for a total of 8400-14400 episodes and 1000-1584 deaths per year. In Spain, the rate of CRBSI has been estimated between 2,1 to 3,4 episodes per 1.000 hospitalized patients[11] .

For instance and according to the surveillance program of nosocomial infections in Catalonia ”VINCat” ,the Catalan hospitals have registered a rate of 0.19 cases by 1000 days of hospital stay, in 47 hospitals with a cost of 39,644 euros per infection causing an additional total cost of 16.055,820 euros in one year only[12]. Table 1 , shows the

absolute number of episodes of CRBSIs throughout the years according to different types of catheters among the Catalan hospitals (VINCat) .

Table 1:The total number of episodes of CRBSIs among different types of catheters from 2008-2017 in Catalunya according to VINCat.

Type of catheter	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
PVC	117	151	154	197	204	129	156	189	178	175
CVC	608	607	461	580	446	405	408	421	371	342
PICC	50	72	70	83	95	80	109	97	129	122

Hypothesis and Objectives

Hypothesis and objectives

Hypothesis

The catheter related bacteremia can be seen as a real threat for the patient's safety and for hospitals. *gram positive bacteria* particularly *S.aureus and* other gram negative microorganisms and yeast can be responsible of these infections. The working hypothesis of this research project reflects on the association of applying effective infections prevention measures with the decrease of the rates of CRBSIs in Bellvitge hospital throughout the period 2003-2016, and the risk factors for mortality associated with CRBSIs among non-ICU patients in the hospital.

Objectives

Main objective:

To describe the epidemiology of CRBSIs and asses the main risk factors for mortality among non-ICU patients with these infections in a tertiary care center. (Bellvitge University Hospital).

Specific objectives

Article I

- To describe the epidemiology of PVCR-BSI in non-ICU patients in a tertiary care center. (Bellvitge University Hospital).
- To describe the impact and the efficacy of a multimodal infection prevention program applied sequentially from 2003 to 2016 aiming to reduce the rates of PVCR-BSI among non ICU patients.
- To decrease the incidence of nosocomial *S.aureus* bacteremia

Article II

- To assess the risk factors for mortality among non- ICU patients with CRBSI in Bellvitge University hospital.

Methods

Methods

In the following section, methods of each article are summarized. Complete methods are described in the articles.

Patients and Setting:

The Bellvitge University Hospital is a 700-bed tertiary care center located in Barcelona area, Spain. An average of 28.000 patients (about 340.000 patient-days) are admitted each year in 31 specialties Units, 9 medical and 22 surgical for a mean length of hospital stay of 8.5 days.

Article I

Study Design: A prospective, longitudinal cohort study was conducted from January 2003 to December 2016, including all adult hospitalized patients with nosocomial PVCR-BSI. Surveillance of PVCR-BSI was standardized throughout the study period and performed in real-time by daily meetings between infection prevention team, infectious diseases staff and microbiologists following confirmation of a bloodstream infection by members of the Microbiology Department. All episodes of bloodstream infections were daily reported by microbiologists, and patients were visited at wards to assess the diagnosis of PVCR-BSI

Definitions: PVCR-BSI was diagnosed according to a slightly modified CDC definition, in a suggestive clinical condition, when growth of concordant bacterial species in a semi-quantitative tip culture and percutaneous draw blood culture was observed, without another apparent source of bacteraemia. In the absence of catheter tip culture, the diagnosis of PVCR-BSI required one or more of the following conditions: a) phlebitis, b) clear resolution of clinical symptoms after catheter withdrawal and a careful exclusion of an alternative explanation for bacteraemia,

Statistical methods: Baseline characteristics of patients were described using mean and standard deviation for continuous variables and frequencies for categorical variables. To test rate trend per year a Poisson regression model was estimated

Article II

Study design:A prospective cohort study was conducted at Bellvitge University Hospital. The primary outcome was 30-day crude mortality among non-ICU patients with nosocomial CRBSIs. Inclusion criteria were as follows: consecutive episodes of nosocomial CRBSIs diagnosed during admission on medical and surgical wards between January 2004 and December 2014. Episodes of bacteraemia were reported daily from the microbiology laboratory to the infection control team. Patients were examined on the wards and those who fulfilled criteria for nosocomial CRBSI were followed-up for 30 days from theonset of bacteraemia and included in a standardized protocol.

Definitions: Days since insertion were defined as the dwelling time from catheter insertion until removal and was also dichotomized into <4 and ≥4 days. Empirical

antibiotic treatment was defined as antibiotics administered within 48 hours of the date on which the first positive blood culture was drawn. Mortality was defined dichotomously as death occurring from any cause within 30 days
of the onset of CRBSI. Patients who remained in hospital after 30 days of CRBSI were counted as alive.

Statistical methods: Continuous variables were compared using the Student's *t*-test or the Mann-Whitney *U*-test, as appropriate. Qualitative and stratified continuous variables were compared using Fisher's exact test or Pearson's chi-squared test.
Time until death was the dependent variable in the Cox regression analysis and was surveyed for 30 days afterthe onset of bacteraemia. Statistical significance was established at $\alpha \leq 0.05$.

Results

Results

In the following section, results of each article are presented. Complete results with the figures and tables are included in the articles.

Article I

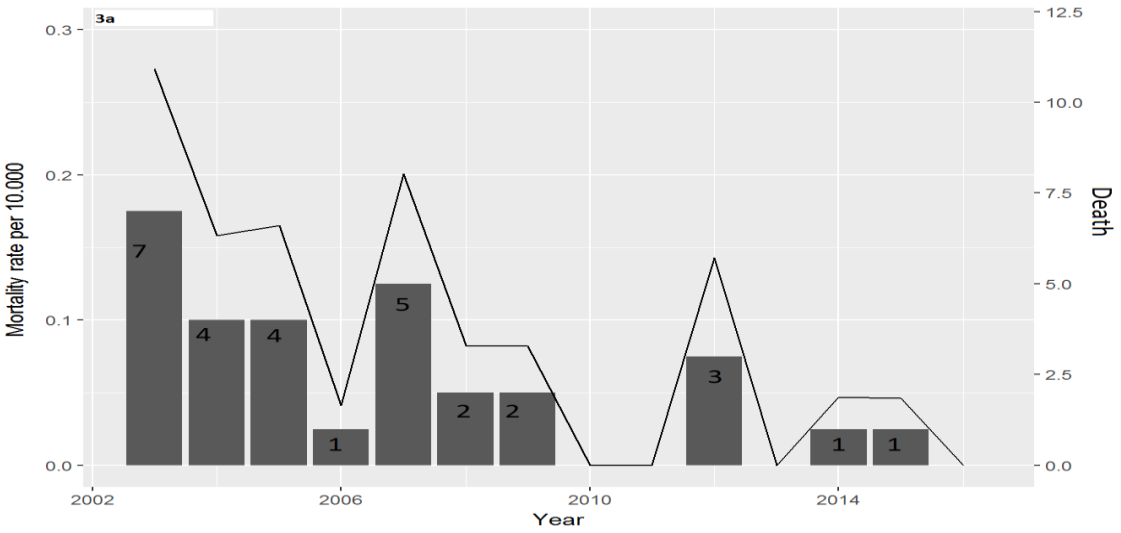
The Characteristics of the episodes

From 2003 to 2016, we identified 227 episodes of PVCR-BSI in non-ICU patients. Mortality was encountered among 13.2% of episodes. *Staphylococcus aureus* was the main responsible organism, accounting for 115 (50.7%) episodes. In the studied population, 156 (68.7%) were males and 147 (64.8%) were >65 y/o.

Impact of the bundles applied

After infection control program implementation, incidence decreased from 30 episodes of PVCR-BSI (1.17 episodes/10,000 patients-days) in 2003 to 8 episodes (0.36 ep/10,000 pt-days) in 2016 with a reduction rate of 8%. Episodes caused by *S.aureus* decreased from 18 episodes in 2003 (0.70 ep/10,000 pt-days) to 3 episodes in 2016 (0.14 ep/10,000 pt-day) with a RR of 9% as well as mortality decreasing from 7 cases in 2003 (0.27ep/10,000 pt days) to 0 cases in 2016 (0.00 ep/10,000 pt days) with a reducti rate of 18% (Figure 2).

Figure 2: Mortality associated to PVCR-BSI and rates per 10,000 hospitalizations from 2003 to 2016



Article II

The characteristics of the episodes

In this study, 546 episodes of CRBSI were diagnosed in 537 non-ICU patients from 2004 to 2014. The infection rate was 0.23/1,000 patient days. 30 days mortality was observed in 76 of 546 episodes (13.9%) and did no vary significantly during the study period (2004-2014). Mortality rates varied according to the presence of co-morbidities, type of ward, type of catheter, place of insertion and etiology.

Risk factors for mortality

When we performed the univariate analysis of factors associated with mortality, the significant factors associated with higher mortality were age ≥65 years, Charlson score ≥4, admission to medical wards, and *S.aureus* or Candida spp. infections. However, when multivariate analysis was performed, we were able to identify a Charlson score ≥4 (HR: 1.80; 95%CI: 1.19-2.73), *S. aureus* infection (HR: 2.67; 95%CI: 1.61-4.43) and Candida spp. (HR: 61; 95%CI: 2.08-18.04) as independent risk factors for mortality.

General Discussion

General Discussion

According to our obtained results and published articles, CRBSIs are a major threat for patient's safety. Among the studied populations, all-cause mortality (within the 30 days from onset of bacteremia) could be up to 13%. Regardless the focus of studies in ICU patients and CVCs, our data have shown that patients carrying PVCs outside ICUs, are at considerable risk of acquiring a CRBSI. Other factors such as a Charlson score of comorbidity ≥4, *S.aureus* and candida spp. infections were independent risk factors associated with mortality. Finally, the application of efficient bundles for PVCR-BSI prevention is able to decrease both the incidence of these episodes and the associated mortality, and the rates of *S.aureus* infections as the major responsible agent of these infections as well.

Prevention program applied: In 2003, BHU introduced an intervention program to prevent CRBSI outside the ICUs. This preventive multi-model was designed by the infectious diseases prevention and control department at BHU, with the support of the Catalan Nosocomial Infection Surveillance Program VINCat[13], a standardized surveillance system providing risk-adjusted, procedure-specific rates of nosocomial infections in Catalonia, Spain. This model was applied sequentially since its implementation in 2003 and it consisted of prevention measures applied for CVCs and PVCs. Recommendations for CVCs included: 1) hand hygiene, 2) preference for a subclavian or jugular insertion site rather than a femoral site, 3) full barrier precautions (sterile full body drape, sterile gown, sterile gloves, hair cover, and mask with eye protection) for insertion, 4) use of 2% Chlorhexidine alcohol solution for skin antisepsis, 5) disinfection of the connector before access, proper maintenance of the dressing and 6) daily review of the need for catheterization. Antibiotic-coated catheters were not used by the VINCaT participating hospitals. Recommendations for PVCs included: 1) hand hygiene, 2) use of 2% alcoholic Chlorhexidine for skin antisepsis, 3) disinfection of the connector prior to access, 4) proper maintenance of the dressing, 5) daily review of the need for catheterization and 6) replacement of short PVCs within 72 h of insertion (or 48 h for those inserted in the emergency department) or in the case of signs of inflammation or extravasation. For both types of catheter, either CVC or PVC, a transparent semipermeable dressing was used to cover the catheter exit site during the study period. The program was promoted

through pocket leaflets and posters placed visibly in all the hospital wards, and through training sessions for the staff. Training sessions were backed up with a prior self-assessment questionnaire containing multiple choice questions on the epidemiology and prevention of CRBSI. Training sessions were backed up with a prior self-assessment questionnaire containing multiple choice questions on the epidemiology and prevention of PV-CRB[14]. Table 2, reflects on some of the items evaluated and the criteria related to asses and prevent PVCR-BSI.

Table 2: Bundle of intervention applied sequentially in BUH to prevent PVCR-BSI.

PERIOD	INFECTION CONTROL INTERVENTION		LEVEL OF EVIDENCE
2003-2005	Continuous surveillance Prevention Program: of PVCR-BSI	Daily meetings of the ICT with microbiology team	IA
		Review of the encountered episodes of PVCRBSI	IA
	Implementation of the Bundle of measures	Introduction of the sterile gloves	Unresolved issue
		Reinforcement of aseptic care technique	IB
		Schedule replacement of peripheral catheters	Unresolved issue
		Skin antisepsis with alcohol base (70%) solution of Chlorhexidine Gluconate (0.5%)	IA
		Extension tube	Unresolved issue
		Semi-permeable dressings for catheters site	IA
	Healthcare workers training	Constant meetings and training sessions for healthcare workers	IA
		Revision of the hospital guidelines for prevention of PVCR-BSI	IA

		Pocket Cards guidelines for hospital staff	IB
		Wallarticles of guidelines for the insertion of peripheral vascular catheters	IB
	Feedback System	Notification to ward staff and discussion with nurse ward team after each case of PVCR-BSI	III
	Upgrade skin antisepsis	Skin antisepsis with alcohol base (70%) or solution of Chlorhexidine Gluconate (2%)	IA
2006-2009	Flushing	Introduction of pre-filled syringes	IV
2010-2016	Upgrade the type and the guidelines for the catheters in use	Introduction of the Closed IV Catheter system	IC
		Unscheduled replacement	IB

The effectiveness of this preventive multi-model program was proved through the results we addressed in Article I. Throughout the years 2003-2016, the application of this preventive protocol was able to decrease the rate of PVCR-BSI of 8% per year and eventually the rates of *S.aureus* associated with PVCR-BSI too, dropping from 16 episodes in 2003 to 3 cases in 2016.

There are few published data on CRBSIs rates outside the ICU. Few previous studies have shown reductions in the rate of CRBSI after introducing specific measures for catheter insertion and maintenance outside the ICU[15]. These studies are based on educational and feedback interventions. The widespread implementation of intervention programs similar to ours could have a major impact on patient safety, with significant reductions in associated morbidity, mortality and cost. Although a recent meta-analysis indicated that routine replacement of peripheral catheters does not reduce the risk of infection[16], the study may have been underpowered to address

the issue of CRBSI because the data analyzed included only 8779 catheter-days, a figure too low to assess a risk of between 0.1 and 0.5 cases per 1000 days. Interestingly, the application of a bundle in an Irish hospital, including the replacement of PVC within 72 h, reduced cases of CRBSI due to *S. aureus* [17]. More recently, a controlled study of education and feedback in Detroit (USA), incorporating a recommendation to replace PVCs within 96 h, obtained a significant reduction in PVCR-BSI[18].

*Etiology***:** Many studies have highlighted that *S.aureus* is the most common and most important pathogen associated with HCAIs and it's highly association with CRBSI. In our studies, rates of SAB varied between 38.8% to 50.7%, these results match with other publications, where *S.aureus* was responsible of 40% of the CRBSI episodes[1]. The pathogenicity of *S.aureus* lead to a high risk for mortality associated with CRBSI. In our study, as described in other previous studies[19], *S.aureus* was associated with a rate of 64.5% mortality associated with CRBSI. The exact incidence of SAB is difficult to ascertain, since prospective population-based surveillance studies are infrequently performed. In Scandinavian countries, where data from the nationwide surveillance of SAB are routinely collected, the annual incidence is approximately 26/100,000 population[20],[21]. A similar low incidence of 19.7/100,000 population was reported in a Canadian study in 2008[22], while in countries with a greater burden of methicillin-resistant *S.aureus* (MRSA), incidence rates are generally higher, between 35 and 39/100,000 population[23], [24]. In comparison, even higher rates, approximately 50/100,000 population, are inferred from surveillance data from the United States[25],[26]. These large geographical discrepancies probably reflect differences in health care systems, infection control practices, and the completeness of surveillance data.

Staphylococcus aureus associated Mortality: Once established, SAB is not a benign condition, resulting in significant morbidity and mortality, especially in intensive care units (ICUs) patients[27],[28]. Interestingly, our research was based on patients outside the ICU, where the mortality associated with SAB was higher than 60% among the patients included in our study. Recent prospective data (2009) of 1,994 SAB episodes suggest that mortality rates may have stabilized, with a 30-day all-cause mortality rate of 20%[29]. Despite these improvements, SAB 30-day all-cause mortality results in approximately 2 to 10 deaths annually per 100,000 population[30],[25]

,[22]. Despite these similar mortality rates, the impact and significance of SAB in the community remain underestimated.

*Risk factors for mortality***:** Besides *S.aureus***,** multiple factors influence CRBSI. These factors include host factors, pathogen-host interactions, and pathogen-specific factors. Most studies analyzing outcomes of patients with CRBSI have been conducted in ICUs and focused on CVC[31]. Mortality attributed to CVC infections in ICUs varies widely according to type of ICU and severity of the underlying disease, ranging from 20% to 50%. Notably, patients with CRBSI were twice as likely to die as patients without CRBSI, after controlling for other hospital-acquired infections and APACHE II scores[32]. A few studies reporting mortality caused by CRBSI have been done outside ICUs[33]. Differences found in the rate of mortality due to CVRBSI among ICU and non-ICU patients could be attributed to the more critically clinical status of ICU patients. Little is known about the factors contributing to CRBSI mortality in non-ICU patients, with few studies having addressed this important issue.

In **Article II** we examined factors that influence mortality and investigated the relative impact of each factor on outcomes for non ICU-patients. The main findings of this article were that CRBSI in non-ICU patients entails significant mortality risk, essentially related to patient comorbidities and etiology. The Cox regression analysis performed in Article II, identified a Charlson score ≥4, *S.aureus* bacteremia and Candida spp. as independent associated factors for CRBSI mortality; while type of catheter, place of insertion and appropriate empirical antibiotic therapy were not identified as independent predictive factors. Our multivariate analysis showed that a Charlson score ≥ 4 was an independent risk factor for mortality among the non-ICU patients with CRBSI and in this population, the mortality rate was as high as 43%.Although only few cases of CRBSI caused by Candida spp. were identified, the mortality rate was as high as 57%, making these yeast species one of the main independent mortality risk factors. Catheter-related bloodstream caused by Candida spp. are more common among ICU patients, where many studies show rates that vary between 36% and 61%[34,35]. In our study, among non-ICU patients, the rate of CRBI due to Candida spp. was 1%; a figure much lower than other observations. For instance, a surveillance study conducted in the USA showed rates of 12% of Candida spp. infections on four medical wards[34]. Sustained low rates of catheter-related

Candidemia in our hospital could be attributed to antimicrobial stewardship policies. In contrast with the etiologies mentioned above, CNS was associated with a low mortality rate of 5.3%.This finding could be explained by the low intrinsic virulence of this group of organisms[36].

On the other hand, interestingly we observed that none of the following factors was associated with higher mortality: the type of catheter, the central compared to peripheral, the place of insertion and the administration of an inadequate empirical antibiotic therapy.

Limitations and strengths

Limitations and strengths

Among all the published studies that can be found in literature, this thesis and its inclusive publications are found to be among the very few work reflecting on PVCR-BSI outside ICU. Although this prospective study covers a large population over a prolonged period of time, it has some limitations that should be acknowledged. The study was performed at a single university hospital; this could mean that our data cannot be extrapolated to other hospitals .This research work is not a randomized study, with the resulting risk of bias due to confounding factors, where the characteristics of our patients, the frequency of catheter use and the frequency of *S. aureus* infections may be different from those observed in other facilities, and thus these factors could account for the results observed in our study .However, we believe that the prospective nature of the study and the proximity in time of the baseline reduce this risk. On the other side, two additional factors that could have some impact on outcomes such as in our study the early removal of the vascular catheter and the presence of septic shock were not analyzed. And finally regarding the presence of septic shock, this variable was not collected in the database.

Conclusions

Conclusions

- At Bellvitge University Hospital, a tertiary care center in Barcelona, Spain, data showed that patients carrying PVCs outside the ICUs are at considerable risk for acquiring a CRBSI.

- Among the non-ICU patients with CRBSI, all-cause mortality (within the 30 days from onset of bacteremia) is up to 13%.

- Charlson score of comorbidity ≥4, *Staphylococcus aureus* and *Candida* spp. were shown as independent risk factors associated with all-cause mortality in such non-ICU patients with CRBSI.

- The application of efficient bundles for PVCR-BSI prevention was able to decrease both the incidence and the associated mortality of these episodes in our non-ICU study population, as well as the rates of *S.aureus* infections as the major responsible organism for these nosocomial infections.

Future perspectives

Future perspectives

Future trends in the evaluation of HCAI should be directed toward a better understanding of the selectivity and specificity of factors underlying opportunistic infections. Several areas of host parasite relations and the hospital environment hold promise for future efforts [37]. They need to be examined individually and collectively as they apply to different aspects of nosocomial infections and selectively relate with different degrees of importance in specific situations.

According to the results of this research work, some major areas are:

1) Detecting and recognizing microbial promoters of clinically important infections and of the interspecies transfer of microbial factors that are advantageous to their proliferation;

2) The future will entail better diagnostic testing to detect the DNA or RNA of resistant organisms at the point of care before culture results, allowing for more targeted therapy, thus reducing resistance[38].

Moreover, future research is expected to give more attention on the prevention of HCAI associated with catheters especially those patients carrying peripheral catheters, as many data including those published in our research study, emphasis the mortality that could be associated with PVCRB-BSI.

Overall, more research must be dedicated to the prevention and detection of nosocomial infections, view the attributed costs, the associated risks on patients safety and healthcare workers, and the burden that these infections impose on the national health system quality outcomes and expenditures.

References

References

1 Gahlot R., Nigam C., Kumar V., Yadav G., Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci* 2014;**4**(2):161. Doi: 10.4103/2229-5151.134184.

2 O'Grady NP., Alexander M., Dellinger EP., et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2002:476–89. Doi: 10.1067/mic.2002.129427.

3 Mermel LA., Allon M., Bouza E., et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**49**(1):1–45. Doi: 10.1086/599376.

4 Shi SH., Kong HS., Jia CK., et al. Coagulase-negative staphylococcus and enterococcus as predominant pathogens in liver transplant recipients with Gram-positive coccal bacteremia. *Chin Med J (Engl)* 2010;**123**(15):1983–8. Doi: 10.3760/cma.j.issn.0366-6999.2010.15.006.

5 Verbrugh HA., Peters R., Goessens WH., Michel MF. Distinguishing complicated from uncomplicated bacteremia caused by Staphylococcus aureus: the value of "new" and "old" serological tests. *J Infect Dis* 1986;**153**(1):109–15.

6 Cherry R a., West CE., Hamilton MC., Rafferty CM., Hollenbeak CS., Caputo GM. Reduction of central venous catheter associated blood stream infections following implementation of a resident oversight and credentialing policy. *Patient Saf Surg* 2011;**5**(1):15. Doi: 10.1186/1754-9493-5-15.

7 Marschall J., Mermel LA., Fakih M., et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;**35**(7):753–71. Doi: 10.1086/676533.

8 Han Z., Liang SY., Marschall J. Current strategies for the prevention and management of central line-associated bloodstream infections. *Infect Drug Resist* 2010;**3**:147–63. Doi: 10.2147/IDR.S10105.

9 Maki DG., Kluger DM., Crnich CJ. The Risk of Bloodstream Infection in Adults With Different Intravascular Devices: A Systematic Review of 200 Published Prospective Studies. *Mayo Clin Proc* 2006;**81**(9):1159–71. Doi: 10.4065/81.9.1159.

10 Tacconelli E, Smith G, Hieke K, Lafuma A, Bastide P. Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature- and registry-based estimates. *J Hosp Infect* 2009;**72**(2):97–103. Doi: 10.

11 Sociedad Española de Medicina Preventiva SP e H. Informe global de España. Análisis EPINE-EPPS 2015. *EPINE* 2015.

12 Departament de Salut Generalitat de Catalunya. Enquesta de salut de Catalunya 2014. Informe dels principals resultats. *2da Ed Barcelona* 2015:1–81.

13 Gudiol F., Limón E., Fondevilla E., Argimon JM., Almirante B., Pujol M. The development and successful implementation of the VINCat Program. *Enferm Infecc Microbiol Clin* 2012;**30**(SUPPL. 3):3–6. Doi: 10.1016/S0213-005X(12)70089-7.

14 Freixas N., Bella F., Limón E., Pujol M., Almirante B., Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: A multicentre study. *Clin Microbiol Infect* 2013;**19**(9):838–44. Doi: 10.1111/1469-0691.12049.

15 Pronovost P., Needham D., Berenholtz S., et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. *N Engl J Med* 2006;**355**(26):2725–32. Doi: 10.1056/NEJMoa061115.

16 Webster J., Osborne S., Rickard CM., New K. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. *Cochrane Database Syst Rev* 2015;**8**:CD007798. Doi: 10.1002/14651858.CD007798.pub4.

17 Bruno M., Brennan D., Redpath MB., et al. Peripheral-venous-catheter-related Staphylococcus aureus bacteraemia: A multi-factorial approach to reducing incidence. *J Hosp Infect* 2011:173–4. Doi: 10.1016/j.jhin.2011.04.026.

18 Fakih MG., Jones K., Rey JE., et al. Sustained Improvements in Peripheral Venous Catheter Care in Non–Intensive Care Units: A Quasi-Experimental Controlled Study of Education and Feedback. *Infect Control Hosp Epidemiol* 2012;**33**(5):449–55. Doi: 10.1086/665322.

19 Fowler VG., Jr., Olsen MK., Corey G., et al. CLinical identifiers of complicated staphylococcus aureus bacteremia. *Arch Intern Med* 2003;**163**(17):2066–72. Doi: 10.1001/archinte.163.17.2066.

20 Benfield T., Espersen F., Frimodt-Møller N., et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. *Clin Microbiol Infect* 2007;**13**(3):257–63. Doi: 10.1111/j.1469-0691.2006.01589.x.

21 Jacobsson G., Dashti S., Wahlberg T., Andersson R. The epidemiology of and risk factors for invasive Staphylococcus aureus infections in western Sweden. *Scand J Infect Dis* 2007;**39**(1):6–13. Doi: 10.1080/00365540600810026.

22 Laupland KB., Ross T., Gregson DB. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. *J Infect Dis* 2008;**198**(3):336–43. Doi: 10.1086/589717.

23 Collignon P., Nimmo GR., Gottlieb T., Gosbell IB. Staphylococcus aureus bacteremia, Australia. *Emerg Infect Dis* 2005;**11**(4):554–561. Doi: 10.3201/eid1104.040772.

24 El Atrouni WI., Knoll BM., Lahr BD., Eckel-Passow JE., Sia IG., Baddour LM. Temporal Trends in Incidence of Staphylococcus aureus Bacteremia in Olmsted County, Minnesota, 1998 to 2005: A Population-based Study. *Clin Infect Dis* 2009;**49**(12):130–8. Doi: 10.1086/648442.Temporal.

25 Klevens RM., Morrison MA., Nadle J., et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *JAMA* 2007;**298**(15):1763–71. Doi: 10.1001/jama.298.15.1763.

26 Morin CA, Hadler JL. 2001. Population-based incidence and characteristics of community-onset Staphylococcus aureus infections with bacteremia in 4 metropolitan Connecticut areas, 1998. J. Infect. Dis.184: 1029–1034

27 Lambert ML., Suetens C., Savey A., et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: A cohort study. *Lancet Infect Dis* 2011;**11**(1):30–8. Doi: 10.1016/S1473-3099(10)70258-9.

28 Shorr AF., Tabak YP., Killian AD., Gupta V., Liu LZ., Kollef MH. Healthcare-associated bloodstream infection: A distinct entity? Insights from a large U.S. database*. *Crit Care Med* 2006;**34**(10):2588–95. Doi: 10.1097/01.CCM.0000239121.09533.09.

29 Turnidge JD., Kotsanas D., Munckhof W., et al. Staphylococcus aureus bacteraemia: a major cause of mortality in Australia and New Zealand. *Med J Aust* 2009;**191**(7):368–73. Doi: tur10849_fm [pii].

30 Asgeirsson H., Kristjansson M., Kristinsson KG., Gudlaugsson O. Staphylococcus aureus bacteraemia--Nationwide assessment of treatment adequacy and outcome. *J Infect* 2011;**62**(5):339–46. Doi: 10.1016/j.jinf.2011.03.003.

31 Ziegler MJ., Pellegrini DC., Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. *Infection* 2015;**43**(1):29–36. Doi: 10.1007/s15010-014-0689-y.

32 Waters M., Nightingale P., Edwards JD. A critical study of the APACHE II scoring system using earlier data collection. *Arch Emerg Med* 1990;**7**(1):16–20. Doi: 10.1136/emj.7.1.16.

33 Rhee Y., Heung M., Chen B., Chenoweth CE. Central Line-Associated Bloodstream Infections in Non-ICU Inpatient Wards: A 2-Year Analysis. *Infect Control Hosp Epidemiol* 2016;**36**(4):424–30. Doi: 10.1017/ice.2014.86.

34 Yapar N. Epidemiology and risk factors for invasive candidiasis. *Ther Clin Risk Manag* 2014;**10**:95–105. Doi: 10.2147/TCRM.S40160.

35 Kett DH., Azoulay E., Echeverria PM., Vincent J-L., Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. Candida bloodstream infections in intensive care units: Analysis of the extended prevalence of infection in intensive care unit study*. *Crit Care Med* 2011;**39**(4):665–70. Doi: 10.1097/CCM.0b013e318206c1ca.

36 Becker K., Heilmann C., Peters G. Coagulase-negative staphylococci. Clin Microbiol Rev 2014;27(4):870–926. Doi: 10.1128/CMR.00109-13

37 Jackson G.G. (1982) Future Trends in Nosocomial Infections: Understanding Selectivity and Specificity in Microbial Opportunism. In: Van Furth R. (eds) Evaluation and Management of Hospital Infections. New Perspectives in Clinical Microbiology, vol 5. Springer, Dordrecht

38 Amin AN., Deruelle D. Healthcare-associated infections, infection control and the potential of new antibiotics in development in the USA. *Futur Microbiol* 2015;**10**(6):1049–62. Doi: 10.2217/FMB.15.33.

Article I

An intervention to decrease short-term peripheral vascular catheter-related bloodstream infections.The impact on incidence and mortality.

Accepted for Publication in Journal of Hospital infection,2018

Interventions to decrease short-term peripheral venous catheter-related bloodstream infections. Impact on the incidence and mortality

Patrick SALIBA[a,e,*], Ana HORNERO[a,d,*], Guillermo CUERVO[a,d], Immaculada GRAU[a,d], Emilio JIMENEZ[a,d], Damaris BERBEL[b,d], Purificación MARTOS[a,d], Juan Manuel VERGE[a,d], Cristian TEBE[d], Jose María MARTÍNEZ-SÁNCHEZ[e], Evelyn SHAW[a,d], Laura GAVALDAc[c,d], Jordi CARRATALÀ[a,d,f], and Miquel PUJOL[a,d].

[a] Department of Infectious Diseases. Bellvitge University Hospital. L'Hospitalet del Llobregat, Barcelona Spain.

[b] Department of Microbiology. Bellvitge University Hospital. L'Hospitalet del Llobregat, Barcelona Spain.

[c] Department of Hospital Hygiene

[d] Bellvitge Biomedical Research Institute (IDIBELL)

[e] Universitat Internacional de Catalunya (UIC). Barcelona, Spain

[f] University of Barcelona. Barcelona, Spain

* PS and AH have contributed equally to work

Corresponding author:

Ana Hornero. Infection Prevention. Infectious Diseases Department. Bellvitge University Hospital.

Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Fax: (+34) 932607637. Phone: (+34) 933357011

e-mail addresses:
patrickuic@uic.es (P. Saliba),
chornero@bellvitgehospital.cat (A. Hornero),
guillermo.cuervo@bellvitgehospital.cat (G. Cuervo)
icgrau@bellvitgehospital.cat (I. Grau)
e.jimenez@bellvitgehospital.cat (E. Jimenez)
dberbelp@bellvitgehospital.cat (D.Berbel)
pmartos@bellvitgehospital.cat (P. Martos)
juanmavm@bellvitgehospital.cat (JM. Verge)
ctebe@idibell.cat (C. Tebe)
jmmartinez@uic.es (J.M. Martinez)
evelyn.shaw@bellvitgehospital.cat (E. Shaw)
lgavalda@bellvitgehospital.cat (L. Gavaldà)
jcarratala@bellvitgehospital.cat (J. Carratalà)
mpujol@bellvitgehospital.cat (M. Pujol)

Running title: Prevention of peripheral venous catheter related bloodstream infections

Summary

Background: Short-term peripheral venous catheters are a significant source of health-care acquired bloodstream infections and a preventable cause of death.

Aim: to assess the effectiveness of interventions applied to reduce the incidence and mortality associated to short peripheral venous catheter-related bloodstream infections (PVCR-BSI).

Methods: The intervention included continuous PVCR-BSI surveillance, implementation of preventive measures targeted to catheter insertion and maintenance according to evidence-based recommendations and hospital's own data, front-line staff educational campaigns, and assessment of adherence to hospital guidelines by ward rounds. *Poisson regression model was used to estimate the trend of rate per year.*

Findings: From January 2003 to December 2016, 227 episodes of PVCR-BSI were identified among hospitalized patients at a university hospital. Mean age: 67y (SD: $\pm$14y), 69% males and median Charlson Score: 3 (interquartile range: 2-5). Among all, *Staphylococcus aureus* caused 115 (50.7%) episodes. Thirty-day mortality was 13.2%. After intervention implementation, incidence decreased significantly from 30 episodes (1.17 episodes/10,000 patient-days) in 2003 to 8 episodes (0.36/10,000 patient-days) in 2016. Episodes caused by *S. aureus* decreased from 18 episodes in 2003 (0.70/10,000 patient-days) to 3 episodes in 2016 (0.14/10,000 patient-day) and mortality decreased from 7 episodes in 2003 (0.27/10,000 patient-days) to 0 episodes in 2016 (0.00 /10,000 patient-days).

Conclusions: Surveillance, implementation of a multimodal strategy and periodical assessment of healthcare personnel adherence to hospital guidelines conduced to a sustained reduction of PVCR-BSIs. This reduction had a major impact among *S. aureus*-BSI rates and associated mortality.

Keywords: Short peripheral venous catheter, bloodstream infections, catheter-related bloodstream infection, mortality, PVCR-BSI, *S.aureus* bloodstream infections

INTRODUCTION

Short-term peripheral venous catheter (PVC) is the most common medical device used in hospitals and a significant source of nosocomial bloodstream infections [1][2]. Despite huge clinical experience using peripheral catheters, there is still a significant controversy over the incidence, clinical impact and preventive measures concerning peripheral venous catheter related-bloodstream infections (PVCR-BSIs) [3].

According to prevalence studies, more than 70% of the hospitalized patients are carriers of a vascular catheter on the day of the study and practically all of them had carried one or more PVC throughout the hospital admission[4]. Furthermore, the use of PVCs has significantly extended inside the health-care system to long-term care facilities and home care. The great number of patients at risk have determined that the possibility of developing an unintended vascular catheter-related adverse event is now much likely to occur than ever before. Significantly, according to data provided by surveillance programs, PVCR-BSIs could be responsible of almost a quarter of vascular catheter-related bloodstream infections[5][6].

Although less frequent than central venous catheter (CVC) related bloodstream infections, PVCR-BSI have distinctive characteristics[7]. The diagnosis is often challenging because of early onset of infections after catheter insertion and because catheter tip culture is infrequently done when catheter is removed for phlebitis or suspicious of infection[8]. Consequently, the diagnosis of PVCR-BSI is often delayed, misdiagnosed as an infusion-related phlebitis until clinical symptoms of sepsis are evident and blood cultures are ultimately taken. This diagnosis delay could be clinically important since the most frequent aetiology is *Staphylococcus aureus* involving a high mortality rate[9][10].

Guidelines for the prevention of vascular catheter infections are mostly focused on CVC and consequently preventive measures for PVC have been inferred from CVC recommendations. Among PVC recommendations, several have low evidence and some others remains unresolved[11]. This has happened because the great majority of catheter-related BSIs surveillance programs have limited to collect data for CVC related bloodstream infections and have systematically ignored cases caused by PVC. Thus, the information available on PVCR-BSIs is much smaller or has directly passed unnoticed.

Because of the establishment at our hospital of an active surveillance program of vascular catheter related BSIs, we were aware since 2003 of a high number of episodes of PVCR-BSI. Episodes were caused by PVC placed in the emergency department as well as in hospital

wards within a few days after insertion entailing a high mortality[7]. This situation encouraged the implementation of a preventive intervention based on published guidelines as well as the analysis of our hospital's own data. Over time, new preventive strategies and new technologies were introduced to achieve a greater reduction in catheter infection rates.

The aim of this study is to examine the effectiveness of this multimodal strategy applied in our centre along a fourteen-year period to prevent PVCR-BSIs.

METHODS

Study design

The Bellvitge University Hospital is a 700-bed tertiary university hospital located in Barcelona area, Spain. An average of 27.000 patients (about 220,000 patient-days) are admitted each year in 37 hospital wards, for a mean length of hospital stay of 8.4 days in 2017. Study Design: A prospective, longitudinal cohort study was conducted from January 2003 to December 2016, including all adult hospitalized patients with nosocomial PVCR-BSI. Surveillance of PVCR-BSI was standardized throughout the study period and performed in real-time by daily meetings between infection prevention team, infectious diseases staff and microbiologists following confirmation of a bloodstream infection by members of the Microbiology Department. All episodes of bloodstream infections were daily reported by microbiologists, and patients were visited at wards to assess the diagnosis of PVCR-BSI. Episodes were recorded in a specific database and patients were followed until thirty days of bloodstream infection or death.

Definitions

PVCR-BSI was diagnosed according to a slightly modified CDC definition, in a suggestive clinical condition, when growth of concordant bacterial species in a semi-quantitative tip culture and percutaneous draw blood culture was observed, without another apparent source of bacteraemia. In the absence of catheter tip culture, the diagnosis of PVCR-BSI required one or more of the following conditions: a) phlebitis, b) clear resolution of clinical symptoms after catheter withdrawal and a careful exclusion of an alternative explanation for bacteraemia. For common skin microorganisms such as coagulase negative Staphylococci (CoNS), at least two consecutive blood cultures were required. Mortality was considered when occurs from any cause within 30 days from the onset of PVCR-BSI.

From 2003 to 2016, the following main outcomes were assessed in a yearly basis: rate of PVCR-BSI (number of PVCR-BSI episodes/10,000 patient-days), rate of *Staphylococcus aureus* PVCR-BSI (number of *Staphylococcus aureus* PVCR-BSI episodes/10,000 patient-days), and rate of mortality within 30 days after the onset of the PVCR-BSI (number of patients who died within 30 days after the episode of PVCR-BSI/10,000 patient-days).

Interventions

The Infection Prevention Team has full responsibilities regarding the prevention and control of vascular catheter-related infections. Since 2003, we were aware of a high incidence of PVCR-BSI in our hospital. To establish the most important characteristics and outline the control measures, we carry out a detailed analysis of episodes[7]. After that, a PVCR-BSI prevention strategy was introduced in a stepwise manner and modified according to surveillance results and new published evidence-base measures. The measures applied along the study period are described in Table I. Main approaches included the following aspects: a) prospective and continuous PVCR-BSI surveillance, b) implementation of preventive measures during catheter insertion and catheter maintenance according to evidence-based recommendations as well as hospital's own data, c) educational campaigns targeted to front-line staff, particularly nurse wards, same day feed-back of PVCR-BSI case to nurse ward supervisor by an electronic advise form, and d) assessment of adherence to preventive strategies by periodical ward rounds performed by a trained infection prevention member who performs an observation of all peripheral vascular catheters, particularly regarding maintenance (insertion site, catheter dressing and connectors), day and area of catheter placement and replacement according to hospital guidelines. The results of observations were provide the same day to the nurse ward supervisor and debated internally in order to improve catheter care.

Statistical methods

Baseline characteristics of patients were described using mean and standard deviation for continuous variables and frequencies for categorical variables. To test rate trend per year a Poisson regression model was estimated. The count of events (PVCR-BSI, S. aureus PVCR-BSI and mortality) was the model dependent variable and number of episodes the offset variable. From the model, the incidence rate ratio per year was reported and interpreted as annual rate increase or decrease. Statistical significance was held at 0.05. All analyses were performed with R version 3.4.1.

Ethical issues

The study was approved by the Ethics Committee at the Bellvitge University Hospital (reference: PR324/15). Informed consent was waived by the Clinical Research Ethics Committee.

RESULTS

From 2003 to 2016, 227 episodes of PVCR-BSI were diagnosed in our study population. Characteristics of patients and episodes are summarized in Table II. Median PVC dwell time form insertion to bloodstream infection was 3 days (interquartile range: 2-5) and did not vary significantly along the study period (Figure 1). Among all, *Staphylococcus aureus* was responsible of 50.7% of episodes and mortality within 30 days of PVCR-BSI was 13.2%.

The PVCR-BSI incidence rates (number of episodes per 10.000 hospital-days) from 2003 to 2016 are shown in Figure 2. After implementing of prevention program, the incidence rate of PVCR-BSI decreased from 30 episodes (1.17 episodes per 10,000 patient-days) in 2003 to 8 episodes (0.34 episodes per 10,000 patient-days) in 2016 with a significant rate reduction of 8% per year. Trends of PVCR-BSI caused by *S. aureus* data are shown in Figure 3. The absolute number of episodes due to *S. aureus* decreased from 18 episodes in 2003 (0.70 episodes per 10,000 patient-days) to 3 episodes in 2016 (0.14 episodes/10,000 patients-day) with a significant rate reduction of 9% per year. Mortality rates along the study period are shown in Figure 4. Mortality significantly decreased from 7 episodes (0.27 episodes per 10,000 patients-days) in 2003 to 0 episodes in 2016 (figure 4) with a significant rate reduction of 18% per year.

Compliance at wards with hospital guidelines regarding catheter care were assessed yearly.

Data of catheter care observations performed during round wards were available from the period 2011-2016 and are shown in Table III.

DISCUSSION

The present study sought to determine the impact of a multimodal bundle of measures applied to prevent PVCR-BSI in our university hospital. These measures were selected according to evidence-based guideline and from a rationale analysis of hospital's own data. Remarkably, the implementation of this bundle of preventive measures along the study period led to a significant reduction in the incidence of PVCR-BSI and associated mortality.

The measures applied were focused on continuous PVCR-BSI surveillance, improvement of PVC insertion and maintenance procedures, educational campaigns targeted to front-line staff, particularly nurse wards, same day feed-back of PVCRI-BSI and assessment of adherence to prevention strategies by periodical ward rounds. The significance of these measures needs to be discussed in deep.

Because PVCR-BSI could represent a significant source of hospital-acquired vascular catheter–related bloodstream infections, continuous surveillance including PVCR-BSI is essential to quantify rates of infections and to identify needs for preventive measures; however, this is still infrequently performed for PVC[12]. Although automated electronic surveillance of healthcare acquired infections is being implemented in many healthcare systems, accuracy of administrative code data for the detection of vascular catheter related infections is low[13]. Therefore, we performed prospective surveillance of PVCR-BSI by trained members of the infection prevention team as described in methods section, even though resources should be allocated by hospital managers to this task. Although manually surveillance could be potentially a source of errors, there is no best available system for PVCR-BSI surveillance to our knowledge. Furthermore, our hospital belongs to a network of health-care infections surveillance system, the VINCat Program[14]. Since 2007, more than 50 centers perform continuous prospective standardized surveillance of PVCR-BSI. Reports from the VINCat program have shown that the incidence of PVCR-BSI in tertiary and secondary care hospitals is much more common than previously expected[6]. Because catheter-related bloodstream infections are considered currently the most preventable healthcare associated infections, it seems essential to implement wide surveillance of vascular catheter related infections including those caused by PVC in most centers[15][16][17].

Our preventive efforts were also focused on high evidence-based measures listed in Table I. Introduction of 2% alcoholic chlorhexidine for skin antisepsis instead of povidone iodine and standardization of the use of semi-transparent polyurethane sterile dressing for short peripheral vascular catheter fixation was easily achieved across all hospital wards. Other measures entailing high workload impact for nurses and incremental costs were implemented

after careful revision of our own data including a debate within the infection prevention team members and the approval of the Hospital Infection Control Committee. These major changes introduced in 2003 included the use of sterile gloves for catheter insertion and mandatory scheduled replacement of short peripheral catheters within 2 days for catheters placed in emergency department and within 3 days for catheters place at hospital wards. Regarding the use of gloves, guidelines still recommend the use of non-touch technique and clean non-sterile gloves for PVC insertion[11]. The reasons to establish mandatory use of sterile gloves during aseptic insertion technique in our hospital were multiple; the high incidence rate of PVCR-BSI observed in our hospital and the frequency of failure in preserving non-touch technique during catheter insertion observed in our hospital and in others, even after training[18].

The evidence that the majority of infections occur within 4 days of insertion, particularly in catheters placed in the emergency department probably area under poor aseptic conditions, and the high frequency of *S.aureus,* commonly found in human skin flora, represents a convincing evidence of contamination during PVC insertion[9]. Furthermore, non-sterile gloves available to healthcare workers for catheter insertion are frequently contaminated by environmental organism including *S. aureus*[19] . For all these reasons the insertion of PVC into the bloodstream system should be done in our opinion with the highest standard of care including sterile gloves.

The scheduled replacement of PVC was introduced in our hospital from 2003 to 2013. The resite of short PVC within 72 hours of placement is still a cause of debate worldwide[3][20][21]. There is no consensus on the optimal time point for PVC change, or whether catheter replacement is required at all, although there is currently an increasing trend towards clinically indicated replacement. No firm recommendation regarding scheduled replacement was performed in the current CDC guidelines[11] and by the Cochrane revision[19], although most of studies found that the median dwell time from insertion to bloodstream infection for PVC particularly for *S. aureus* infections was equal or more than 4 days[9]. Randomized studies analysing the risk of bloodstream infections have shown no benefit of replacing PVC every 72h compare to unscheduled replacement [20]. However, these results should be analysed with caution. Although the incidence of PVCR-BSI appears low compared to CVC the absolute numbers of PVCR-BSI could be high[3]. Catheter replacement within 48 hours for catheters placed in the emergency department and within 72 hours for catheters placed at hospital wards has been highly reached in our hospital according to data showed in table III. This measure has significantly contributed to the reduction of PVCR-BSI rates in our hospital during the period it has been implemented.

The hospital policy of scheduled replacement of peripheral catheters placed in hospital wards changed in 2013 after the introduction of a closed safety peripheral intravenous catheter system into the clinical practice[22]. The material of the catheter is a determining factor in the development of phlebitis[23] and the introduction of new catheter materials could be important to decrease the risk of phlebitis and bloodstream infections. All the current information comes from last decade [24],[25] although the risk of adverse events could be different according to the different type and design of peripheral catheters currently available. The unscheduled catheter replacement since 2013 allowed us to improve the patient's well-being, a reduction in invasive procedures and a decrease in the nurse workload preserving the reduction of PCVR-BSI obtained previously.

Finally, educational campaigns performed by members of the infection prevention team explaining changes at all hospital wards were early introduced in 2003. It was considered essential to explain the reasons for protocol changes to all front-line professionals. Later, ward rounds were regularly performed to review the implementation of control measures followed by a dialogue of problems observed during these rounds. This practice established an interaction between leads of the infection prevention team and healthcare workers from wards that was considered essential to achieve all the changes proposed[26]. The immediate feedback of results to ward nurse personnel every time that a case of PVCR-BSI was detected, with a root-cause analysis, allowed us to raise awareness of the problem and the need to implement at maximum the prevention measures, since attending nursing staff were infrequently aware of PVCR-BSI because this information were not usually translated from medical team to nurse ward team.

It is also important to recognize the limitations of our study. This study has been carried out in a single center and although the characteristics of PVCR-BSI are similar to those observed in other centers, the frequency of infections and the impact of measures could vary. It is also important to recognize that some of the applied measures did not fullfill the current clinical practice guidelines for PVC management, although they have been considered to have been highly effective in our environment. Also, when different prevention measures are applied simultaneously it is difficult to distinguish which of them has been more effective. On the other hand, one of the main strengths of our study is the prolonged period of study, the high number of cases evaluated and the high understanding of this problem by the experienced team of infection prevention. In conclusion, PVCR-BSI is a much more common problem in hospitals than previously suspected, involving high morbidity and mortality rates. The implementation of a multimodal strategy and continuous assessment of performance

conduced to a sustained reduction of PVCR-BSI. This reduction had a major impact among *S.aureus* associated PVCR-BSI rates and mortality.

Competing Interests

The authors have no competing interests to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

[1] Sato A, Nakamura I, Fujita H, Tsukimori A, Kobayashi T, Fukushima S, et al. Peripheral venous catheter-related bloodstream infection is associated with severe complications and potential death: A retrospective observational study. BMC Infect Dis 2017;17. doi:10.1186/s12879-017-2536-0.

[2] Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, et al. The european centre for disease prevention and control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Eurosurveillance 2012. doi:10.2900/86011.

[3] Mermel LA. Short-term Peripheral Venous Catheter-Related Bloodstream Infections: A Systematic Review. Clin Infect Dis 2017;65:1757–62. doi:10.1093/cid/cix562.

[4] Zhang L, Cao S, Marsh N, Ray-Barruel G, Flynn J, Larsen E, et al. Infection risks associated with peripheral vascular catheters. J Infect Prev 2016;17:207–13. doi:10.1177/1757177416655472.

[5] Karchmer AW. Bloodstream infections: the problem and the challenge. Int J Antimicrob Agents 2009;34:S2–4. doi:10.1016/S0924-8579(09)70556-4.

[6] Limon E, Pujol M, Gudiol F. [Validation of the structure and resources of nosocomial infection control team in hospitals ascribed to VINCat program in Catalonia, Spain]. Validacion La Estruct y Los Recur Los Equipos Control La Infecc Nosocom En Los Hosp Del Programa VINCat En Catalunya 2014;143 Suppl:43–7. doi:10.1016/j.medcli.2014.07.010.

[7] Pujol M, Hornero A, Saballs M, Argerich MJ, Verdaguer R, Cisnal M, et al. Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital. J Hosp Infect 2007;67:22–9. doi:10.1016/j.jhin.2007.06.017.

[8] Guembe M, Pérez-Granda MJ, Capdevila JA, Barberán J, Pinilla B, Martín-Rabadán P, et al. Nationwide study on peripheral-venous-catheter- associated-bloodstream infections in internal medicine departments. J Hosp Infect 2017;97:260–6. doi:10.1016/j.jhin.2017.07.008.

[9] Stuart RL, Cameron DRM, Scott C, Kotsanas D, Grayson ML, Korman TM, et al. Peripheral intravenous catheter-associated Staphylococcus aureus bacteraemia: more than 5 years of prospective data from two tertiary health services. Med J Aust 2013;198:551–3.

[10] Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, García D, et al. Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study. J Hosp Infect 2018;99:48–54.

doi:10.1016/j.jhin.2017.11.002.

[11] O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1–29. doi:10.1039/c1ee02165f.

[12] Zingg W, Sax H, Inan C, Cartier V, Diby M, Clergue F, et al. Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. J Hosp Infect 2009;73:41–6. doi:10.1016/j.jhin.2009.05.015.

[13] Goto M, Ohl ME, Schweizer ML, Perencevich EN. Accuracy of administrative code data for the surveillance of healthcare-associated infections: A systematic review and meta-analysis. Clin Infect Dis 2014;58:688–96. doi:10.1093/cid/cit737.

[14] Gudiol F, Limón E, Fondevilla E, Argimon JM, Almirante B, Pujol M. The development and successful implementation of the VINCat Program. Enferm Infecc Microbiol Clin 2012;30:3–6. doi:10.1016/S0213-005X(12)70089-7.

[15] Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the Proportion of Healthcare-Associated Infections That Are Reasonably Preventable and the Related Mortality and Costs. Infect Control Hosp Epidemiol 2011;32:101–14. doi:10.1086/657912.

[16] Van Mourik MSM, Perencevich EN, Gastmeier P, Bonten MJM. Designing Surveillance of Healthcare-Associated Infections in the Era of Automation and Reporting Mandates. Clin Infect Dis 2018;66:970–6. doi:10.1093/cid/cix835.

[17] Mitchell BG, Russo PL. Preventing healthcare-associated infections: the role of surveillance. Nurs Stand 2015;29:52–8. doi:10.7748/ns.29.23.52.e9609.

[18] Fakih MG, Jones K, Rey JE, Takla R, Szpunar S, Brown K, et al. Peripheral venous catheter care in the emergency department: Education and feedback lead to marked improvements. Am J Infect Control 2013;41:531–6. doi:10.1016/j.ajic.2012.07.010.

[19] Hughes KA, Cornwall J, Theis JC, Brooks HJL. Bacterial contamination of unused, disposable non-sterile gloves on a hospital orthopaedic ward. Australas Med J 2013;6:331–8. doi:10.4066/AMJ.2013.1675.

[20] Webster J, Osborne S, Rickard CM, New K. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. Cochrane Database Syst Rev 2015;8:CD007798. doi:10.1002/14651858.CD007798.pub4.

[21] Safdar N, McKinley LM, Davidson B, Broome C, Schenk J. Recommendations to replace peripheral venous catheters every 72-96 hours: Is a single reference enough? J Hosp Infect 2011;79:172–3. doi:10.1016/j.jhin.2011.06.005.

[22] González López JL, Arribi Vilela A, Fernández del Palacio E, Olivares Corral J, Benedicto Martí C, Herrera Portal P. Indwell times, complications and costs of open vs

closed safety peripheral intravenous catheters: A randomized study. J Hosp Infect 2014;86:117–26. doi:10.1016/j.jhin.2013.10.008.

[23] Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters: A randomized controlled trial. Ann. Intern. Med., vol. 114, 1991, p. 845–54. doi:10.7326/0003-4819-114-10-845.

[24] Jacquot C, Fauvage B, Bru JP, Croize J, Calop J. Peripheral venous catheterization: influence of catheter composition on the occurrence of thrombophlebitis. vol. 8. 1989.

[25] Karadağ a, Görgülü S. Effect of two different short peripheral catheter materials on phlebitis development. J Intraven Nurs 2000;23:158–66.

[26] Knobloch MJ, Chewning B, Musuuza J, Rees S, Green C, Patterson E, et al. Leadership rounds to reduce health care-associated infections. Am J Infect Control 2017. doi:10.1016/j.ajic.2017.08.045.

Table I: Bundle of intervention applied sequentially in BUH to prevent PVCR-BSI.

PERIOD	INFECTION CONTROL INTERVENTION		LEVEL OF EVIDENCE
2003-2005	Continuous surveillance of PVCR-BSI	Daily meetings of the ICT with microbiology team	IA
		Review of the encountered episodes of PVCRBSI	IA
	Implementation of the Bundle of measures	Introduction of the sterile gloves	Unresolved issue
		Reinforcement of aseptic care technique	IB
		Schedule replacement of peripheral catheters	Unresolved issue
		Skin antisepsis with alcohol base (70%) solution of chlorhexidinegluconate (0.5%)	IA
		Extension tube	Unresolved issue
		Semi-permeable dressings for catheters site	IA
	Healthcare workers training	Constant meetings and training sessions for healthcare workers	IA
		Revision of the hospital guidelines for prevention of PVCR-BSI	IA
		Pocket Cards guidelines for hospital staff	IB
		Wallpapers of guidelines for the insertion of peripheral vascular catheters	IB
	Feedback System	Notification to ward staff and discussion with nurse ward team after each case of PVCR-BSI	III
	Upgrade skin antisepsis	Skin antisepsis with alcohol base	IA

		(70%) or solution of chlorhexidinegluconate (2%)	
2006-2009	Flushing	Introduction of pre-filled syringes	IV
2010-2016	Upgrade the type and the guidelines for the catheters in use	Introduction of the Closed IV Catheter system	IC
		Unscheduled replacement	IB

Table II: Clinical epidemiology and microbiology of PVCR-BSI

Variables	**2003-2005 N=71**	**2006-2009 N=78**	**2010-2016 N=78**	**Overall N=227**
Male	44 (62%)	55 (70.5%)	57 (73.1%)	156 (68.7%)
Age >65	38 (53.57%)	58 (74.4%)	51 (65.4%)	147 (64.8%)
Area				
Medical	51 (71.8%)	35 (44.9%)	38 (48.7%)	124 (54.6%)
Surgery	20 (28.2%)	43 (55.1%)	40 (51.3%)	103 (45.4%)
Median (IQ) dwell time (Insertion to BSI)	4 (IQ:3-6)	4 (IQ:3-7)	5 (IQ:3-6)	**4 (IQ:3-6)**
Microorganisms				
Gram positive	63 (88.7%)	55 (70.5%)	55 (70.5%)	173 (76.2%)
Gram negative bacili	9 (12.7%)	22 (28.8%)	21 (26.9%)	52 (22.9%)
Staphylococcus aureus	41(57.7%)	39 (50%)	35 (44.9%)	115 (50.7%)
MSSA (a)	34 (47.9%)	36 (46.6%)	28 (35.9%)	98 (43.2%)
MRSA (b)	7 (9.9%)	3 (3.8%)	7 (9%)	17 (7.5%)
Coagulase negative staphylococci	22 (31%)	15 (19.2%)	19 (24.4%)	56 (24.7%)
Enterococcus spp	0%	1 (1.3%)	1 (1.3%)	2 (0.9%)
A.baumannii (c)	0%	3 (3.8%)	1 (1.3%)	4 (1.8%)
P.aeruginosa (d)	0%	1 (1.3%)	2 (2.6%)	3 (1.3%)
Candida spp	0%	1 (1.3%)	0%	1 (0.4%)

Charlson > 4	45 (63.4%)	32 (41%)	33 (42.3%)	100 (48.5%)
30 days mortality (episodes)/10,000 pt-days	**15 (21.1%)**	**10 (12.8%)**	**5 (6.4%)**	30 (13.21%)

(a) Meticillin susceptible S. Aureus
(b) Meticillin-resistant *S. Aureus*
(c) *Acinetobacter baumannii*
(d) *Pseudomonas aeruginosa*

Table III:Assessment of PVC care

Assessment of PVC catheter care						
	2011 (n=492)	**2012 (n=490)**	**2013 (n=487)**	**2014 (n=495)**	**2015 (n=485)**	**2016 (n=669)**
ED[1] placement	65 (13.21%)	62 (12.65%)	68 (13.96%)	63 (12.72%)	51 (10.51%)	64 (9.56%)
48h Replacement	56 (86.15%)	55 (88.7%)	64 (94.11%)	62 (98.41%)	49 (96.07%)	62 (96.87%)
HW[2] placement	427 (86.79%)	428 (87.35%)	419 (86.04%)	432 (87.28%)	434 (89.49%)	605 (90.44%)
72h Replacement	407 (95.31%)	406 (94.85%)	409 (97.61%)	420 (97.22%)	418 (96.31%)	603 (99.66%)
Dressing	475 (96.54%)	477 (97.34%)	479 (98.35%)	481 (97.17%)	476 (98.14%)	660 (98.65%)
Catheter site	470 (95.52%)	468 (95.51%)	470 (96.5%)	476 (96.16%)	474 (97.73%)	655 (97.90%)
Extension tube	472 (95.93%)	473 (96.53%)	471 (96.71%)	482 (97.37%)	479 (98.76%)	655 (97.90%)
Absence of phlebitis	489 (99.39%)	488 (99.59%)	486 (99.79%)	492 (99.39%)	484 (99.79%)	666 (99.5%)
Absence of extravasation	489 (99.39%)	489 (99.79%)	487 (100%)	495 (100%)	485 (100%)	669 (100%)
Clinical chart registration	483 (98.17%)	483 (98.57%)	481 (98.76%)	490 (98.98)	479 (98.76%)	668 (99.85%)
TOTAL	95.8%	96.36%	97.72%	98.08%	98.19%	98.79%

1. ED: Emergency Department
2. HW: Hospitalization Ward

Figure 1: Mean days of catheterization

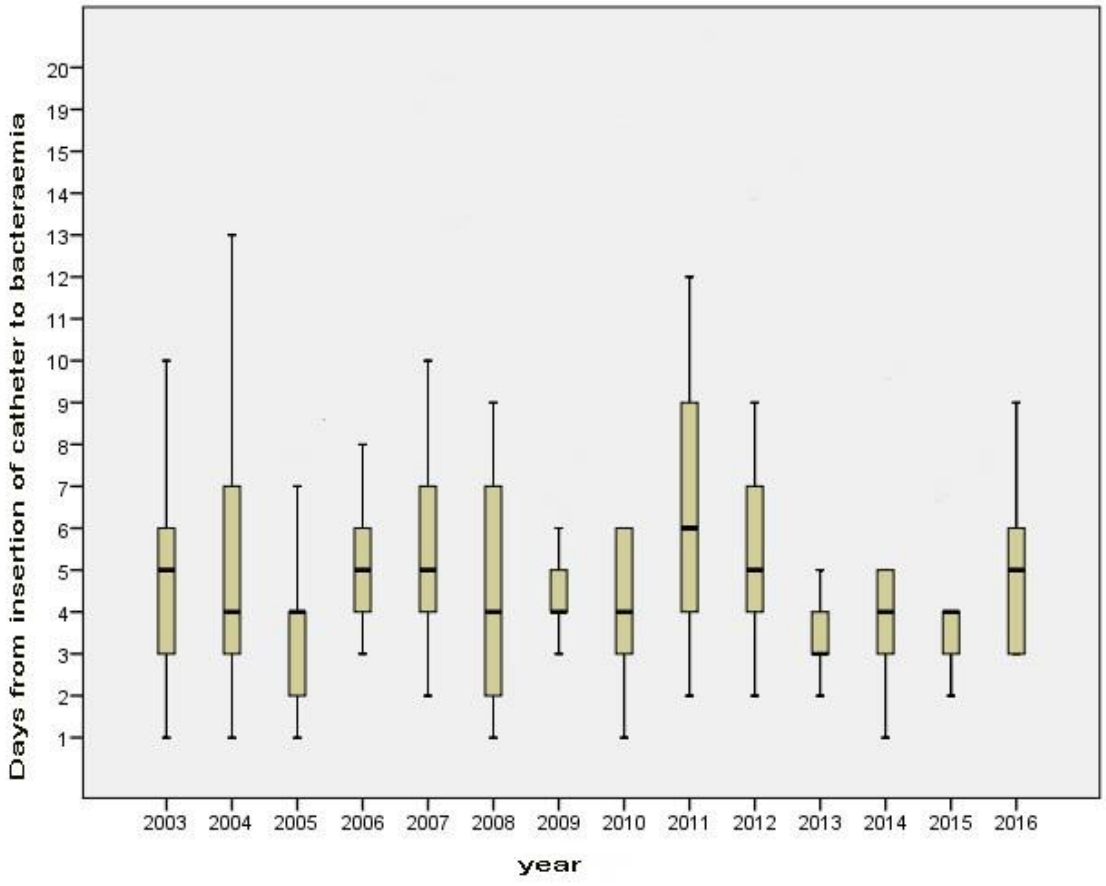
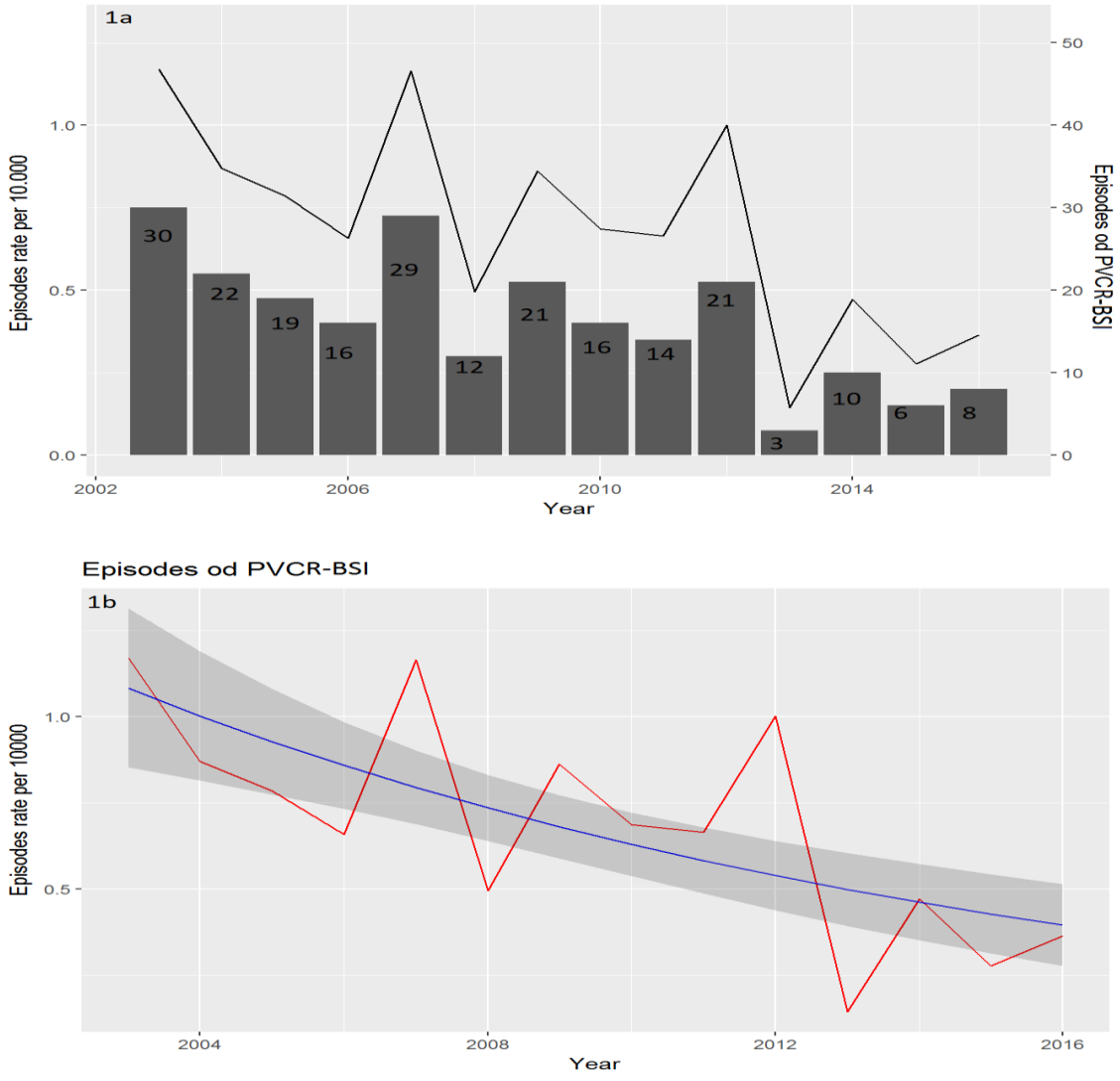
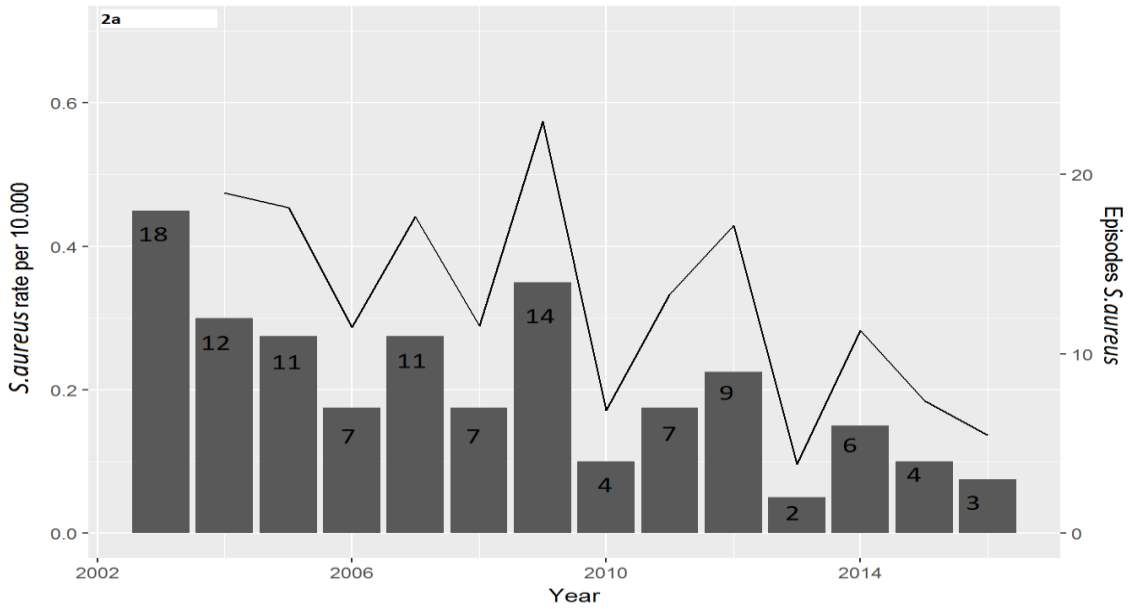


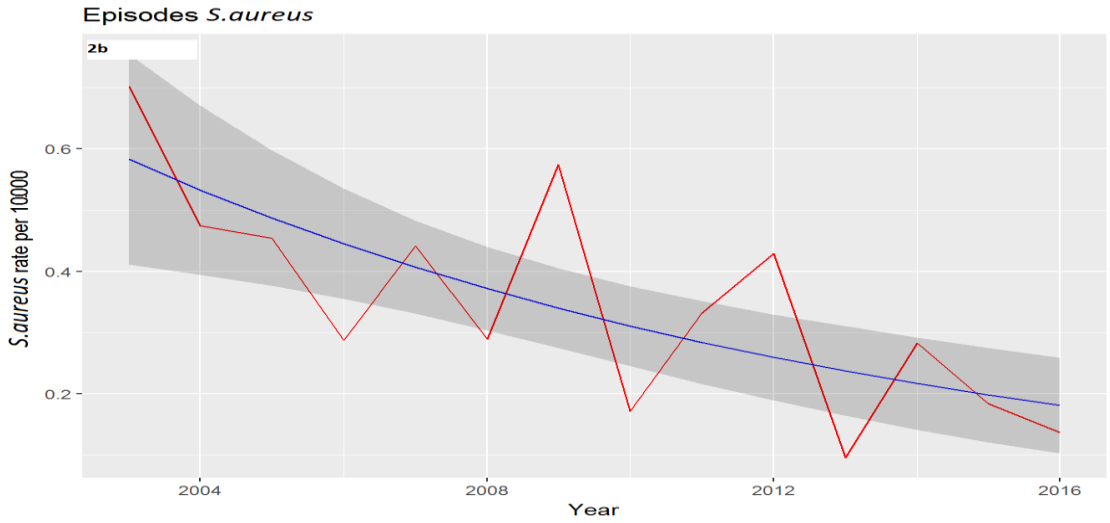
Figure 2: Episodes of PVCR-BSI and rates per 10000 hospitalizations from 2003 to 2016.



Risk rate of 0.92 (95%CI:0.90-0.96)

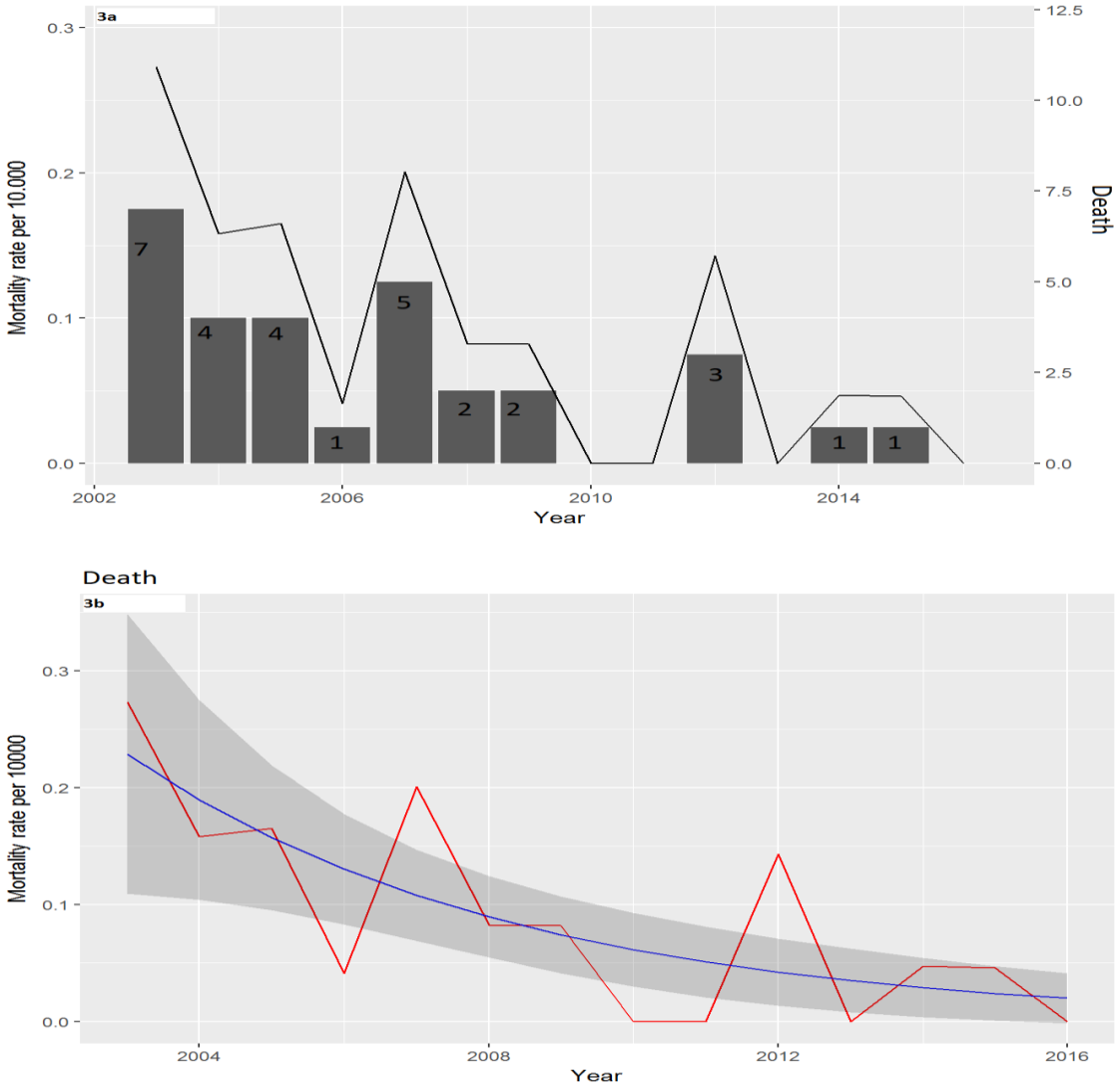
Figure 3: S.aureus associated with PVCR-BSI episodes and rates per 10000 hospitalizations from 2003 to 2016.





Risk rate of 0.91 (95%CI:0.86-0.96)

Figure 4: Mortality episodes and rates per 10000 hospitalizations from 2003 to 2016.



Risk rate of 0.82 (%95CI:0.74-0.91)

Legends

Figure 1a: the bars represent the observed episodes of PVCRB and the lines show the observed rates by 10.000 hospitalizations.

Figure 1b: In red, observe the rates and in blue the predicted ones by a Poisson regression model. Estimated risk rate per one year increase is 0.92 (95%CI: 0.90-0.96) representing a statistical significant reduction of 8% on PVCRB rate per year.

Figure 2a: the bars represent the observed episodes of S.aureus and the lines show the observed rates by 10.000 hospitalizations.

Figure 2b: In red,we observe the rates and in blue the predicted ones by a Poisson regression model. Estimated risk rate per one year increase is 0.91 (95%CI:0.86-0.96) representing a statistical significant reduction of 9% on S.aureus rate per year.

Figure 3a: the bars represent the observed episodes of mortality and the lines show the observed rates by 10.000 hospitalizations.

Figure 3b: In red, we observe the rates and in blue the predicted ones by a Poisson regression model. Estimated risk rate per one year increase is 0.82 (%95CI:0.74-0.91) representing a statistical significant reduction of 18% on mortality rate per year.

Article II

Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study.

Published in Journal of Hospital infection, 2017

Risk factors of mortality among non-ICU patients with vascular catheter-related bacteraemia. A prospective cohort study

Patrick SALIBA[a,c], Ana HORNERO[a,d], Guillermo CUERVO[a], Immaculada GRAU[a], Emilio JIMENEZ[a,d], Dolors GARCÍA[b], Fe TUBAU[b], Jose María MARTÍNEZ-SÁNCHEZ[c], Jordi CARRATALÀ[a,d], and Miquel PUJOL[a,d].

[a] Department of Infectious Diseases. Hospital Universitari de Bellvitge. Institut d'Investigació Biomèdica de Bellvitge (IDIBELL). University of Barcelona, Barcelona, Spain

[b] Department of Microbiology. Hospital Universitari de Bellvitge. Barcelona, Spain

[c] Universitat Internacional de Catalunya (UIC). Barcelona, Spain

[d] VINCat Program. Barcelona, Spain

Corresponding author:

Miquel Pujol. Infectious Diseases Department. University hospital of Bellvitge. Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat,Barcelona, Spain. Fax: (+34) 932607637. Phone: (+34) 933357011

e-mail addresses:

patrickuic@uic.es (P.Saliba),

jcarratala@bellvitgehospital.cat (J. Carratalà)

guillermocuervo@hotmail.com (G.Cuervo)

chornero@bellvitgehospital.cat (A. Hornero),

e.jimenez@bellvitgehospital.cat (E.Jimenez)

jmmartinez@uic.es (J.M.Martinez)

icgrau@bellvitgehospital.cat (I.Grau)

f.tubau@bellvitgehospital.cat (F. Tubau)

dsomoza@bellvitgehospital.cat (D. Garcia)

mpujol@bellvitgehospital.cat (M. Pujol)

Running title: Risk factors for CRBSI mortality

SUMMARY

Background

Vascular catheter-related bloodstream infection (CRBSI) is currently considered the most preventable hospital-acquired infection and a major threat for patient safety. While we have much information regarding the epidemiology and outcomes of CRBSI among Intensive Care Unit (ICU) patients, data is scarce in non-ICU patients.

Objective: To determine risk factors for 30-days mortality among non-ICU patients with hospital-acquired CRBSI.

Methods and Study Design: Prospective cohort study of non-ICU patients with nosocomial CRBSI. Setting and period of study: Tertiary-care centre, from January 2004 to December 2014. Main outcome: Crude mortality defined as death of any cause within 30 days of CRBSI. CRBSI follow-up: 30-days since data of BSI. Time until death was the dependent variable in Cox regression analysis.

Findings: A total of 546 episodes of CRBSI were identified; mean age 64.5y (IQR:55-75), 66% males and mean Charlson score 3.59 (IQR:2-5). Among all, 58.4% carried a central venous catheter and 41.6% peripheral venous catheter. Gram-positive cocci caused 70.1% of episodes, Gram-negative bacilli 31.1% and Candida spp.1%. Mortality within 30 days occurred in 76 of 546 patients (13.9%). Charlson score ≥4 (HR:1.80; 95%CI:1.19-2.73), *Staphylococcus aureus* infection (HR:2.67; 95%CI:1.61-4.43) and Candida spp. (HR:6.1; 95%CI:2.08-18.04) were identified as independent risk factors for CRBSI mortality, while age, area of admission, type, use and place of vascular catheter, and appropriate empirical antibiotic treatment were not.

Conclusion: Nosocomial CRBSIs in patients outside ICUs carry a high risk of death particularly among those patients with higher Charlson score and bloodstream infection caused by *S. aureus* and Candida spp.

Key words

Catheter-related bloodstream infections
Risk factors for mortality
Staphylococcus aureus

INTRODUCTION

Vascular catheters are the most commonly used medical devices in hospitals[1,2,3]. According to a large European prevalence study[4], almost 55% of hospitalized patients carried a vascular catheter during the study and virtually all of them needed one or more vascular catheters during their hospitalization. Although in non-intensive care units (ICUs) catheter utilization is lower than in ICUs, the total burden of vascular catheters in use is higher in the non-ICU setting.

Adverse events related to vascular catheterization are frequent. Catheter-related bloodstream infection (CRBSI) are among the most serious complications, causing high morbidity, mortality and a rise in hospital costs[5]. The incidence of CRBSI varies according to type and characteristics of the vascular catheter and the insertion site[6]. Rates of CRBSI are higher for central venous catheters (CVCs) than for peripheral venous catheters (PVCs)[7], although given the number of patients exposed to PVCs, the absolute number of PVC-BSI can be significant. Remarkably, CRBSI has become the most preventable cause of healthcare-related infections[8] and in fact, over the last decade, the implementation of a bundle of interventions to prevent CRBSI has led to a significant and sustained reduction in the incidence of CRBSI, particularly in ICUs[9,10].

While most studies have focused on the epidemiology of CRBSI, particularly CVC-related bloodstream infections in the ICU setting, little information is available on the epidemiology and outcomes of CRBSI outside ICUs. The objective of this study was to determine the risk factors for mortality among patients with nosocomial CRBSI in non-critically-ill patients hospitalized in medical and surgical wards.

METHODS

Setting

The Bellvitge University Hospital is a 700-bed tertiary teaching hospital located in the Barcelona area, Spain. Each year, an average of 28,000 patients are admitted (around 340,000 patient-days) in 31 specialty units, 9 medical and 22 surgical wards for a mean length of hospital stay of 8.5 days. Patients with previously diagnosed haematological or solid malignancies as a cause of admission are transferred to a specific cancer healthcare setting.

Study design and patients population

A prospective cohort study of all consecutive episodes of nosocomial CRBSI diagnosed in hospitalized adult patients during admission on medical and surgical wards, excluding ICUs, was performed from January 2004 to December 2014. Throughout the study period, CRBSI surveillance was performed by daily meetings of the Infection Control Team with members of the Microbiology Department.

Episodes of bacteraemia were reported daily from the microbiology laboratory. Patients were visited in wards and those who fulfilled criteria for nosocomial CRBSI were followed for 30 days from the onset of the CRBSI and included in a standardized protocol for further analysis. Removal of a transient vascular catheter with suspected infection is a routine practice in our hospital. Isolates considered contaminants were not the subject of this study.

Definitions

CRBSI was diagnosed in any patient with clinical signs and symptoms of sepsis according the definition of the Infectious Diseases Society of America (IDSA)[11] when a growth of concordant bacterial species in a semi-quantitative tip culture and blood culture was observed, without another obvious source of the bacteraemia.

In the absence of a catheter tip culture, the diagnosis of CRBSI required either of the following conditions: i) phlebitis, or ii) clear resolution of clinical symptoms after catheter withdrawal and a careful exclusion of an alternative explanation for bacteraemia. For common skin microorganisms such as coagulase-negative staphylococci (CoNS), at least two consecutive blood cultures were required with the same species and identical susceptibility pattern to indicate possible CRBSI.

Co-morbidity was measured using the Charlson score, as described elsewhere [12]. The Charlson score was dichotomized for the purpose of the analysis into two categories: < 4 and ≥ 4 points. Days since insertion was defined as the dwell time from catheter insertion until removal and it was also dichotomized into <4 and ≥ 4 days. The empirical antibiotic was defined as the one administered within 48 hours of the date on which the first positive blood culture was drawn, and it was considered appropriate if the strain was susceptible to at least one of the antibiotics administered according to the current Clinical and Laboratory Standards Institute (CLSI) breakpoints[13].

Mortality was defined dichotomously as death occurring from any cause within 30 days of the onset of CRBSI. Patients who remained admitted at the hospital after 30 days of CRBSI were counted as alive. Attributable mortality was not recorded to avoid subjectivity in determining cause of death.

Microbiology identification and susceptibility testing

Two sets of two blood samples were collected from patients with a suspected bloodstream infection. The blood samples were processed using a BACTEC 9240 system (Becton–Dickinson Microbiology Systems, New Jersey, USA), with an incubation period of 5 days at 35ºC before being discharged. If bacteria were observed after microscopic Gram stain examination, blood bottles were subcultured onto Chocolate agar plates.

Catheter tips were cultured after removal, as described elsewhere [14]. The tip was rolled 3 to 4 times on a blood agar plate, which was incubated at 37ºC for 48 hours and then analysed. The presence of ≥ 15 colony-forming units was considered evidence of local catheter infection. The identification and antibiotic susceptibility of Gram-negative bacilli (GNB) and *Enterococcus* spp. were performed using commercial panels from the MicroScan system (Beckman Coulter, Inc). Viridans group streptococci (VGS) were identified using standard methods [15]. Antibiotic susceptibility testing to determine the minimal inhibitory concentration (MICs) was performed by a microdilution method using commercial panels from Sensititre TM system (TREK Diagnostic Systems Ltd). Identification of other Gram-positive cocci (GPC) including CoNS was performed using standard methods and antibiotic susceptibility was determined using a disc diffusion method, according to the recommendations of CLSI. EUCAST and/or CLSI criteria were used to define susceptibility or resistance to antimicrobial agents [13,16].

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Mann-Whitney *U*-test as appropriate. Qualitative and stratified continuous variables were compared using Fisher's exact test or Pearson's chi-squared test. Relative risks were calculated with 95% confidence intervals in univariate analysis. Time until death was the

dependent variable in Cox regression analysis and was surveyed for 30 days after the onset of bacteraemia. Statistical significance was established at $\alpha \leq 0.05$. All the variables that achieved a p value of ≤ 0.05 in the univariate analysis were included in multivariate analysis. The chi-squared test for trend in proportions was performed to determine significant variations in mortality during the study period.

For variables significantly associated with mortality, a Kaplan-Meier curve was plotted to show the survival probabilities at 30 days. All the analysis was performed using SPSS software v.15 (SPSS Inc., Chicago, Illinois, USA).

Ethical issues

The study was approved by the Ethics Committee at the Bellvitge University Hospital (reference: PR324/15). Informed consent was waived by the Clinical Research Ethics Committee.

RESULTS

Characteristics of episodes

During the study period, 546 episodes of CRBSI were diagnosed in 537 non-ICU patients: 297(54%) in surgical wards and 249(46%) in medical wards. The infection rate was 0.23/1,000 patient days. The characteristics of the episodes are summarized in Table I. Mortality was observed in 76 of 546 episodes (13.9%) and did no vary significantly during the study period. Mortality rates varied according to the presence of co-morbidities, type of ward, type of catheter, place of insertion and aetiology (Table I).

The univariate analysis of factors associated with mortality is shown in Table I. Significant factors associated with higher mortality were age ≥65 years, Charlson

score ≥4, and admission to medical wards, *S. aureus* or Candida spp. infections. The Cox regression analysis (Table II) identified a Charlson score ≥4 (HR:1.80; 95%CI:1.19-2.73), *Staphylococcus aureus* infection (HR:2.67; 95%CI:1.61-4.43) and Candida spp. (HR:6.1; 95%CI:2.08-18.04) as independent mortality risk factors. Figure 1, shows the Kaplan-Meier survival curves for Charlson score ≥ 4, *S. aureus,* and Candida spp. that were statistically significant factors associated with mortality in the bivariate analysis.

DISCUSSION

The main findings of our study are that CRBSI outside ICUs is frequent and entails significant mortality, essentially related to patient co-morbidities and aetiology. Several surveillance studies have suggested that CRBSI rates could be similar in both ICU and non-ICU settings [17,18]. Most studies analysing mortality in patients with CRBSI have been conducted in ICUs and focused on CVC[19]. Mortality attributed to CVC infections in ICUs varies widely depending on type of ICU and severity of the underlying disease, ranging from 20% to 50%[19]. Notably, patients with CRBSI were twice as likely to die as patients without CRBSI, after controlling for other hospital-acquired infections and APACHE II scores[20]. In contrast, in non-ICU settings, few studies are reported and the number of cases included in the studies is limited. Few studies performed outside ICUs addressed CVC and did not include CRBSI caused by short PVC. However, BSI related to short PVC is an important under-recognised problem among non-ICU patients and a significant cause of mortality [21,22]. Furthermore, rates of CRBSI and mortality outside ICUs are often underestimated when hospital-wide surveillance does not include all types of venous catheters, both central and peripheral.

A few studies reporting mortality caused by CRBSI have been done outside ICUs. A study performed in an 880-bed tertiary teaching hospital focused on central line infections found a CRBSI rate of 0.35/1,000 patient days and a mortality rate of 18.3% [23]. This rate of mortality was slightly higher than what we observed, because patients with underlying malignancy and neutropenia were included; whereas in our case, those patients were usually transferred to a specific cancer facility. Differences in the rate of mortality among ICU and non-ICU patients could be attributed to the more critically clinical status of ICU patients.

Little is known about the factors contributing to CRBSI mortality in non-ICU patients, with few studies having addressed this important issue. The Cox regression analysis identified a Charlson score≥4, *S. aureus* infection or Candida spp. as independent predictive factors for CRBSI mortality; while type of catheter, place of insertion and appropriate empirical antibiotic therapy were not identified as independent predictive factors. The Charlson score was developed as a prognostic index to predict 1-year mortality among patients admitted to the medical service of an acute care hospital[24].Our multivariate analysis showed that a Charlson score ≥ 4points was an independent risk factor for mortality among the non-ICU patients with CRBSI. In these patients the mortality rate was 43%.

In our study, we identified *S. aureus* as the microorganism most frequently associated with higher mortality among non-ICU patients, with a mortality rate of 23%. Our results correlate with various studies where *S. aureus* has been reported to be associated with mortality rates ranging from 15% to 60% [25]. Although only few cases of CRBSI caused by Candida spp. were identified, the mortality rate was as high as 57%, making these yeast species one of the main independent mortality risk factors. Catheter-related bloodstream caused by Candida spp. are more common among ICU patients, where many studies show rates that vary between 36% and 61% [26,27]. In our study, among non-ICU patients, the rate of CRBI due to Candida spp. was 1%; a figure much lower than other observations. For instance, a surveillance study conducted in the USA showed rates of 12% of Candida spp. infections on four medical wards[28]. Sustained low rates of catheter-related candidemia in our hospital could be attributed to a strict antimicrobial stewardship policy applied since early 2000.

Interestingly, we observed that none of the following factors was associated with higher mortality: the type of catheter, the central compared to peripheral place of insertion and the administration of an inadequate empirical antibiotic therapy.

Although this prospective study covers a large population over a prolonged period of time, it has some limitations that should be acknowledged. The study was performed at a single university hospital; this could mean that our data cannot be extrapolated to other hospitals. In addition to the characteristics of our patients, the frequency of catheter use and the frequency of *S. aureus* infections may be different from those observed in other facilities, and thus these factors could account for the results observed in our study

As a final remark, the results of our study reinforce the importance of implementing programs for the control of CRBSI in non-critically ill patients, as is the case for critically ill patients. These programs have been successfully implemented in different scenarios and could lead to a reduction in CRBSI mortality[29,30].

In conclusion, great attention should be paid to non-ICU patients with CRBSI, a high Charlson score and *S. aureus* or Candida spp. aetiology.

Competing Interests

The authors have no competing interests to declare.

Transparency declarations

The authors declare that they have no competing interests.

Authors' Contributions

PS was involved in data collection, data analysis and writing the manuscript. AH and IG were involved in data collection and discussion of the results. GC was involved in data analysis, discussion of the results and writing the manuscript. EJ was involved in data collection and discussion of the results. DG and FT were involved in microbiological analysis and discussion of the results. JC contributed with intellectual input and manuscript discussion. MP offered intellectual input and expertise and was involved in each phase of the study. All the authors read and approved the final version of the manuscript.

Acknowledgements

Writing assistance was provided by the Department of Languages of the Faculty of Medicine of University of Barcelona and the manuscript was fully revised by the Language Services of the same university.

REFERENCES

1 Lederle FA., Parenti CM., Berskow LC., Ellingson KJ. The idle intravenous catheter. *Ann Intern Med* 1992;**116**(9):737–8.

2 Waitt C., Waitt P., Pirmohamed M. Intravenous therapy. *Postgrad Med J* 2004;**80**(939):1–6.

3 Ritchie S., Jowitt D., Roberts S., Auckland District Health Board Infection Control Service. The Auckland City Hospital Device Point Prevalence Survey 2005: utilisation and infectious complications of intravascular and urinary devices. *N Z Med J* 2007;**120**(1260):U2683.

4 Zarb P., Coignard B., Griskeviciene J., et al. The european centre for disease prevention and control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveill* 2012. Doi: 10.2900/86011.

5 Stevens V., Geiger K., Concannon C., et al. Inpatient costs, mortality and 30-day re-admission in patients with central-line-associated bloodstream infections. *Clin Microbiol Infect* 2014;**20**(5):O318-24. Doi: 10.1111/1469-0691.12407.

6 Maki DG., Kluger DM., Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc* 2006;**81**(9):1159–71. Doi: 10.4065/81.9.1159.

7 Pujol M., Hornero A., Saballs M., et al. Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital. *J Hosp Infect* 2007;**67**(1):22–9. Doi: 10.1016/j.jhin.2007.06.017.

8 Ferrer C., Almirante B. [Venous catheter-related infections]. *Enferm Infecc Microbiol Clin* 2014;**32**(2):115–24. Doi: 10.1016/j.eimc.2013.12.002.

9 Palomar M., Álvarez-Lerma F., Riera A., et al. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. *Crit Care Med* 2013;**41**(10):2364–72. Doi: 10.1097/CCM.0b013e3182923622.

10 Freixas N., Bella F., Limón E., Pujol M., Almirante B., Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: a multicentre study. *Clin Microbiol Infect* 2013;**19**(9):838–44. Doi: 10.1111/1469-0691.12049.

11 Mermel LA., Allon M., Bouza E., et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**49**(1):1–45. Doi: 10.1086/599376.

12 Charlson ME., Pompei P., Ales KL., MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**(5):373–83.

13 CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. *Clin Lab Stand Inst* 2013;**32**:1–184.

14 Maki DG., Weise CE., Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med* 1977;**296**(23):1305–9. Doi: 10.1056/NEJM197706092962301.

15 Peel MM., Alfredson DA., Gerrard JG., et al. Isolation, identification, and molecular characterization of strains of Photorhabdus luminescens from infected humans in Australia. *J Clin Microbiol* 1999;**37**(11):3647–53.

16 Jean S-S., Liao C-H., Sheng W-H., Lee W-S., Hsueh P-R. Comparison of commonly used antimicrobial susceptibility testing methods for evaluating susceptibilities of clinical isolates of Enterobacteriaceae and nonfermentative Gram-negative bacilli to cefoperazone–sulbactam. *J Microbiol Immunol Infect* 2015. Doi: 10.1016/j.jmii.2015.08.024.

17 Kallen AJ., Patel PR., O'Grady NP. Preventing Catheter-Related Bloodstream Infections outside the Intensive Care Unit: Expanding Prevention to New Settings. *Clin Infect Dis* 2010;**51**(3):335–41. Doi: 10.1086/653942.

18 Zingg W., Sax H., Inan C., et al. Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. *J Hosp Infect* 2009;**73**(1):41–6. Doi: 10.1016/j.jhin.2009.05.015.

19 Ziegler MJ., Pellegrini DC., Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. *Infection* 2015;**43**(1):29–36. Doi: 10.1007/s15010-014-0689-y.

20 Waters M., Nightingale P., Edwards JD. A critical study of the APACHE II scoring system using earlier data collection. *Arch Emerg Med* 1990;**7**(1):16–20. Doi: 10.1136/emj.7.1.16.

21 Zingg W., Pittet D. Peripheral venous catheters: an under-evaluated problem. *Int J Antimicrob Agents* 2009;**34**:S38–42. Doi: 10.1016/S0924-8579(09)70565-5.

22 Stuart RL., Cameron DRM., Scott C., et al. Peripheral intravenous catheter-associated Staphylococcus aureus bacteraemia: more than 5 years of prospective data from two tertiary health services. *Med J Aust* 2013;**198**(10):551–3.

23 Rhee Y., Heung M., Chen B., Chenoweth CE. Central Line-Associated Bloodstream Infections in Non-ICU Inpatient Wards: A 2-Year Analysis. *Infect Control Hosp Epidemiol* 2015;**36**(4):424–30. Doi: 10.1017/ice.2014.86.

24 Gagne JJ., Glynn RJ., Avorn J., Levin R., Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol* 2011;**64**(7):749–59. Doi: 10.1016/j.jclinepi.2010.10.004.

25 Ladhani S., Konana OS., Mwarumba S., English MC. Bacteraemia due to Staphylococcus aureus. *Arch Dis Child* 2004;**89**:568–71. Doi: 10.1136/adc.2003.026781.

26 Leroy O., JP G., Montravers P., et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). *Crit Care Med* 2009;**37**(5):1612–1618 7p. Doi: 10.1097/CCM.0b013e31819efac0.

27 Kett DH., Azoulay E., Echeverria PM., Vincent J-L., Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. Candida bloodstream infections in intensive care units: Analysis of the extended prevalence of

infection in intensive care unit study*. *Crit Care Med* 2011;**39**(4):665–70. Doi: 10.1097/CCM.0b013e318206c1ca.

28 Yapar N. Epidemiology and risk factors for invasive candidiasis. *Ther Clin Risk Manag* 2014;**10**:95–105. Doi: 10.2147/TCRM.S40160.

29 García-Rodríguez JF., Álvarez-Díaz H., Vilariño-Maneiro L., et al. Epidemiology and impact of a multifaceted approach in controlling central venous catheter associated blood stream infections outside the intensive care unit. *BMC Infect Dis* 2013;**13**(1):445. Doi: 10.1186/1471-2334-13-445.

30 Castagna HMF., Kawagoe JY., Gon????alves P., et al. Active surveillance and safety organizational goals to reduce central line???associated bloodstream infections outside the intensive care unit: 9 years of experience. *Am J Infect Control* 2016;**44**(9):1058–60. Doi: 10.1016/j.ajic.2016.02.034.

Table I: Predictive factors for mortality due to CRBSI (univariate analysis)

	Overall N=546 (%)	Alive n=470 (%)	Dead n=76 (%)	P value (*)
Age (≥65y)	306 (56)	255 (54.3)	51 (67.1)	0.046
Male gender	358 (66)	307 (65.3)	51 (67.1)	0.796
Charlson score ≥4	244 (44.9)	193 (41.3)	51 (67.1)	0.001
Area of Admission:				
Medical ward	249 (45.6)	204 (43.4)	45 (59.2)	0.013
Surgical ward	297 (54.4)			
Days since insertion<4	81 (14.8)	71 (15.1)	10 (13.2)	0.405
Use of catheter				
Fluid, medication	351 (64.3)	300 (63.8)	51 (67.1)	0.117
Parenteral nutrition	115 (14.7)	105 (22.3)	10 (13.2)	0.218
Haemodialysis	80 (14.7)	65 (13.8)	15 (19.7)	0.105
Type of catheter:				
Peripheral	227 (41.6)	200 (42.6)	27 (35.5)	0.466
Short peripheral	134 (25.1)	114 (24.9)	20 (26.7)	0.467
Midline	63 (11.8)	57 (12.4)	6 (8)	0.284
Central	319 (58.4)	270 (57.4)	49 (64.5)	0.152
Subclavian	105 (19.2)	90 (19.1)	15 (19.7)	0.876
Jugular	97 (17.8)	84 (17.9)	13 (17.1)	1.000
Femoral	64 (11.7)	52 (11.1)	12 (15.8)	0.249
PICC	52 (9.5)	43 (9.1)	9 (11.8)	0.526
Type of microorganisms				

Gram-positive bacteria	383 (70.1)	321 (68.3)	62 (81.6)	0.021

	Hazard ratio	95%CI	P value
Charlson score ≥4	1.803	1.19- 2.73	0.005

Staphylococcus aureus	212 (38.8)	163 (34.7)	49 (64.5)	0.001
MRSA	41 (7.5)	26 (5.5)	15 (19.7)	0.001
MSSA	171 (31.3)	137 (29.1)	34 (44.7)	0.008
Coagulase-negative staphylococci	150 (27.5)	142 (30.2)	8 (10.5)	0.001
Enterococci	25 (4.6)	20 (4.3)	5 (6.6)	0.373
Gram-negative bacilli	170 (31.1)	154 (32.8)	16 (21.1)	0.045
Klebsiella pneumoniae	42 (7.7)	40 (8.5)	2 (2.6)	0.070
Pseudomonas aeruginosa	38 (7)	31 (6.6)	7 (9.2)	0.463
Acinetobacter baumannii	10 (1.8)	10 (2.1)	0 (0)	0.371
Candida spp.	7 (1.3)	3 (0.6)	4 (5.3)	0.009
Appropriate treatment	331 (61.6)	282 (60.9)	49 (66.2)	0.440

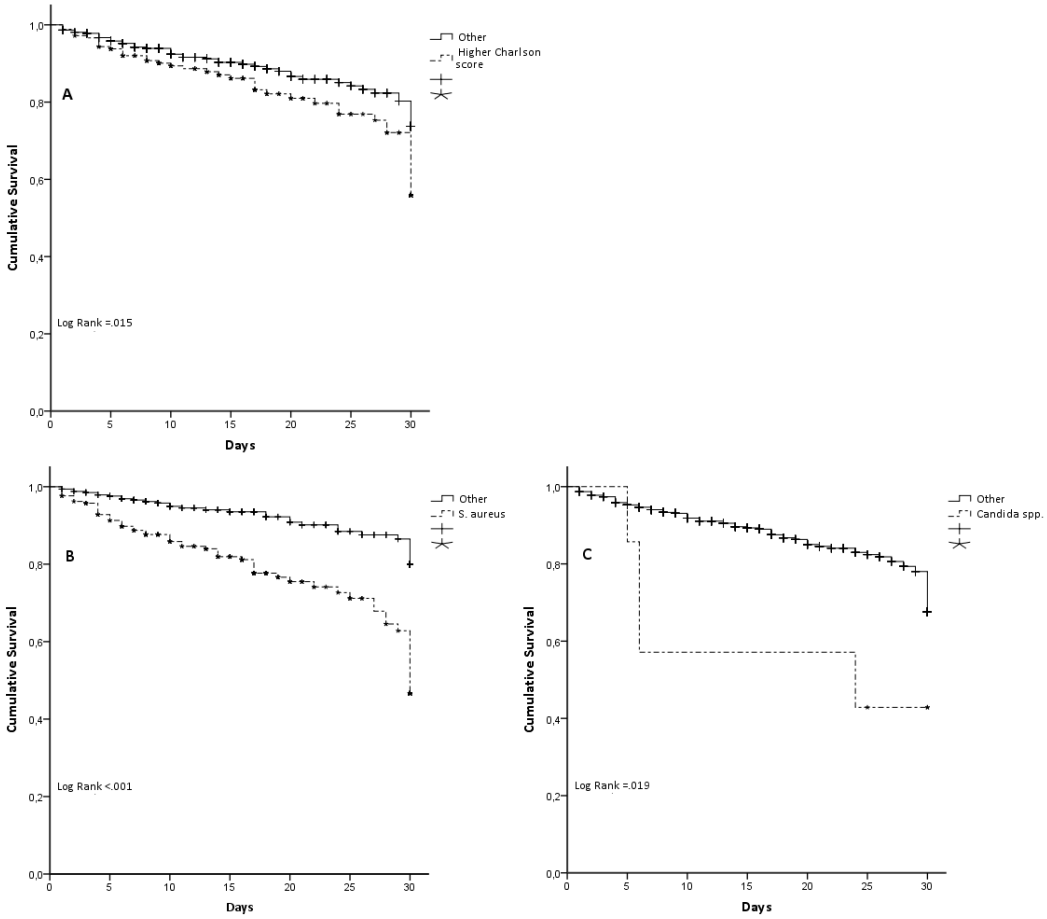
SD: standard deviation, PICC: peripherally inserted central catheter, *MRSA: methicillin*-resistant staphylococcus aureus, MSSA: methicillin-sensitive Staphylococcus aureus, Candida spp.: Candida species, *P-value refers to the comparison betweenaliveand dead.

Table II: Multivariate analysis for mortality (Cox-regression)

S. aureus	2.673	1.61- 4.43	<0.001
Candida. spp.	6.133	2.08- 18.04	<0.001

S.aureus: Staphylococcus aureus, Candida. spp.*: Candida species,* 95%CI: 95%confidence interval

Figure 1



A: Charlson score (≥4) **B:** *Staphylococcus aureus* CRBSI. **C:** *Candida spp.*CRBSI.

Legends

Figure 1: Kaplan-Meier survival curves for Charlson score ≥ 4, *S. aureus,* and Candida spp. that were statistically significant factors associated with mortality in the bivariate analysis.

Annexes

Annex I

Accepted Manuscript

Interventions to decrease short-term peripheral venous catheter-related bloodstream infections. Impact on incidence and mortality

Patrick saliba, Ana hornero, Guillermo cuervo, Immaculada grau, Emilio jimenez, Damaris berbel, Purificación martos, Juan Manuel verge, Cristian TEBE, Jose María martínez-sánchez, Evelyn shaw, Laura gavaldà, Jordi carratalà, Miquel pujol

PII: S0195-6701(18)30324-4

DOI: 10.1016/j.jhin.2018.06.010

Reference: YJHIN 5461

To appear in: *Journal of Hospital Infection*

Received Date: 14 May 2018

Accepted Date: 11 June 2018

Please cite this article as: saliba P, hornero A, cuervo G, grau I, jimenez E, berbel D, martos P, Manuel verge J, TEBE C, María martínez-sánchez J, shaw E, gavaldà L, carratalà J, pujol M, Interventions to decrease short-term peripheral venous catheter-related bloodstream infections. Impact on incidence and mortality, *Journal of Hospital Infection* (2018), doi: 10.1016/j.jhin.2018.06.010.

Interventions to decrease short-term peripheral venous catheter-related bloodstream infections. Impact on incidence and mortality

Patrick SALIBA[a,e,*], Ana HORNERO[a,d,*], Guillermo CUERVO[a,d], Immaculada GRAU[a,d], Emilio JIMENEZ[a,d], Damaris BERBEL[b,d], Purificación MARTOS[a,d], Juan Manuel VERGE[a,d], Cristian TEBE[d], Jose María MARTÍNEZ-SÁNCHEZ[e], Evelyn SHAW[a,d], Laura GAVALDÀ[c,d], Jordi CARRATALÀ[a,d,f], and Miquel PUJOL[a,d].

[a] Department of Infectious Diseases. Bellvitge University Hospital. L'Hospitalet del Llobregat, Barcelona Spain.

[b] Department of Microbiology. Bellvitge University Hospital. L'Hospitalet del Llobregat, Barcelona Spain.

[c] Department of Preventive Medicine-Hospital Hygiene

[d] Bellvitge Biomedical Research Institute (IDIBELL)

[e] Universitat Internacional de Catalunya (UIC). Barcelona, Spain

[f] University of Barcelona. Barcelona, Spain

* PS and AH have contributed equally to this study

Corresponding author:

Ana Hornero. Infection Prevention. Infectious Diseases Department. Bellvitge University Hospital.

Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Fax: (+34) 932607637. Phone: (+34) 933357011

E-mail addresses:

patrickuic@uic.es (P. Saliba)

chornero@bellvitgehospital.cat (A. Hornero)

guillermo.cuervo@bellvitgehospital.cat (G. Cuervo)

icgrau@bellvitgehospital.cat (I. Grau)

e.jimenez@bellvitgehospital.cat (E. Jimenez)

dberbelp@bellvitgehospital.cat (D.Berbel)

pmartos@bellvitgehospital.cat (P. Martos)

juanmavm@bellvitgehospital.cat (JM. Verge)

ctebe@idibell.cat (C. Tebe)

jmmartinez@uic.es (J.M. Martinez)

eshawp@gmail.com (E. Shaw)

lgavalda@bellvitgehospital.cat (L. Gavaldà)

jcarratala@bellvitgehospital.cat (J. Carratalà)

mpujol@bellvitgehospital.cat (M. Pujol)

Running title: Prevention of peripheral venous catheter related bloodstream infections

Summary

Background: Short-term peripheral venous catheters are a significant source of health-care acquired bloodstream infections and a preventable cause of death.

Aim: To assess the effectiveness of interventions applied to reduce the incidence and mortality associated with short peripheral venous catheter-related bloodstream infections (PVCR-BSI).

Methods: The intervention included continuous PVCR-BSI surveillance, implementation of preventive measures related to catheter insertion and maintenance in accordance with evidence-based recommendations and the hospital's own data, front-line staff educational campaigns, and assessment of adherence to hospital guidelines by ward rounds. A Poisson regression model was used to estimate the trend of rate per year.

Findings: From January 2003 to December 2016, 227 episodes of PVCR-BSI were identified among hospitalized patients at a university hospital. Mean age: 67y (SD: ±14y), 69% males and median Charlson Score: 3 (interquartile range: 2-5). Among all, *Staphylococcus aureus* caused 115 (50.7%) episodes. Thirty-day mortality was 13.2%. After the implementation of the intervention, incidence decreased significantly from 30 episodes (1.17 episodes/10,000 patient-days) in 2003 to eight (0.36/10,000 patient-days) in 2016. Episodes caused by *S. aureus* fell from 18 in 2003 (0.70/10,000 patient-days) to three in 2016 (0.14/10,000 patient-day) and mortality fell from seven cases in 2003 (0.27/10,000 patient-days) to zero in 2016 (0.00 /10,000 patient-days).

Conclusions: Surveillance, implementation of a multimodal strategy and periodical assessment of healthcare personnel adherence to hospital guidelines led to a sustained reduction in PVCR-BSIs. This reduction had a major impact on *S. aureus*-BSI rates and associated mortality.

Keywords: Short peripheral venous catheter, bloodstream infections, catheter-related bloodstream infection, mortality, PVCR-BSI, *S.aureus* bloodstream infections

INTRODUCTION

Short-term peripheral venous catheter (PVC) is the most common medical device used in hospitals and a significant source of nosocomial bloodstream infections [1,2]. Despite vast clinical experience using peripheral catheters, significant controversy remains regarding the incidence and clinical impact of peripheral venous catheter related-bloodstream infections (PVCR-BSIs) and regarding the design of measures to prevent them [3].

According to prevalence studies, more than 70% of hospitalized patients have a vascular catheter in situ on the day of the study and practically all have received one or more PVCs at some point during their hospital admission [4]. Furthermore, the use of PVCs has spread significantly throughout the health-care system and has now extended to long-term care facilities and home care. Because of the large number of patients at risk, the likelihood of developing an unintended vascular catheter-related adverse event is now much higher than ever before. Significantly, according to data provided by surveillance programmes, PVCR-BSIs may be responsible for almost a quarter of vascular catheter-related bloodstream infections [5,6].

Although less frequent than central venous catheter (CVC)-related bloodstream infections, PVCR-BSI have distinctive characteristics [7]. Diagnosis is often challenging because of the early onset of infections after catheter insertion and because catheter tip culture is rarely performed when the catheter is removed for phlebitis or the suspicion of infection [8]. Consequently, the diagnosis of PVCR-BSI is often delayed, or it is misdiagnosed as an infusion-related phlebitis until clinical symptoms of sepsis are evident and blood cultures are finally taken. This delay in diagnosis may have clinical repercussions since the most frequent aetiology is *Staphylococcus aureus,* which has a high mortality rate [9,10].

Guidelines for the prevention of vascular catheter infections focus mostly on CVC, and so preventive measures for PVC have been inferred from CVC recommendations. Among PVC recommendations, several are based on low quality evidence and the value of others remains unclear [11]. This is because the great majority of catheter-related BSIs surveillance programmes have been limited to collecting data for CVC-related bloodstream infections and have systematically ignored cases caused by PVC. Thus, the information available on PVCR-BSI is much more restricted or has passed unnoticed.

Since the introduction of an active surveillance programme of vascular catheter-related BSIs at our hospital in 2003, we have recorded a high number of episodes of PVCR-BSI. These episodes develop within a few days of the insertion of PVCs in the emergency department or in hospital wards, entailing high mortality [7]. This situation led us to design a preventive intervention based on published guidelines and on the analysis of our hospital's own data. Over time, new preventive strategies and new technologies have been introduced in order to reduce catheter infection rates still further.

The aim of this study is to examine the effectiveness of this multimodal strategy applied at our centre to prevent PVCR-BSIs over a 14-year period.

METHODS

Study design

The Bellvitge University Hospital is a 700-bed tertiary university hospital located in Barcelona, Spain. A mean of 27,000 patients (about 220,000 patient-days) are admitted each year in 37 hospital wards. In 2017, the mean length of hospital stay was 8.4 days. A prospective, longitudinal cohort study was conducted from January 2003 to December 2016, including all adult hospitalized patients with nosocomial PVCR-BSI. Surveillance of PVCR-BSI was standardized throughout the study period and performed in real-time by daily meetings between the infection prevention team, infectious diseases staff and microbiologists following confirmation of a bloodstream infection by members of the Microbiology Department. All episodes of bloodstream infections were reported daily by microbiologists, and patients were visited in the wards to assess the diagnosis of PVCR-BSI. Episodes were recorded in a specific database and patients were followed until thirty days after bloodstream infection or death.

Definitions

PVCR-BSI was diagnosed according to a slightly modified CDC definition, in a suggestive clinical condition, when the growth of concordant bacterial species in a semi-quantitative tip culture and percutaneously drawn blood culture was observed, without another apparent source of bacteraemia (12). In the absence of a catheter tip culture, the diagnosis of PVCR-BSI required one or more of the following conditions: a) phlebitis, b) clear resolution of clinical symptoms after catheter withdrawal, and c) careful exclusion of an alternative explanation for bacteraemia. For common skin microorganisms such as coagulase negative staphylococci (CoNS), at least two consecutive blood cultures were required. Mortality was considered when it occurred due to any cause within 30 days of the onset of PVCR-BSI.

From 2003 to 2016, the following main outcomes were assessed on a yearly basis: rate of PVCR-BSI (number of PVCR-BSI episodes/10,000 patient-days), rate of *Staphylococcus aureus* PVCR-BSI (number of *S. aureus* PVCR-BSI episodes/10,000 patient-days), and rate of mortality within 30 days of the onset of the PVCR-BSI (number of patients who died within 30 days of the episode of PVCR-BSI/10,000 patient-days).

Interventions

The Infection Prevention Team has full responsibilities regarding the prevention and control of vascular catheter-related infections. Since 2003, we have been aware of a high incidence of PVCR-BSI in our hospital. To establish the most important characteristics and to outline the control measures, we carried out a detailed analysis of the episodes [7]. After this, a PVCR-BSI prevention strategy was introduced in a stepwise manner and modified according to the surveillance results and newly published evidence-base measures. The measures applied during the study period are displayed in Table I. The approaches included the following steps: a) prospective and continuous PVCR-BSI surveillance, b) implementation of a specific bundle for insertion and maintenance of PVC according to evidence-based recommendations as well as the hospital's own data, c) educational campaigns targeted at front-line staff, particularly nurse wards, same-day notification of the PVCR-BSI case to the nurse ward supervisor via an electronic form, and d) assessment of adherence to preventive strategies by periodical ward rounds performed by a trained infection prevention member who inspected all peripheral vascular catheters, focusing particularly on maintenance (insertion site, catheter dressing and connectors), the day, and the area of catheter placement and replacement according to hospital guidelines. The results of the observations were given on the same day to the nurse ward supervisor and discussed internally in order to improve catheter care.

Statistical methods

Baseline characteristics of patients were described using means and standard deviation for continuous variables and frequencies for categorical variables. To test the rate trend per year, a Poisson regression model was estimated. The number of events (PVCR-BSI, *S. aureus* PVCR-BSI and mortality) was the model's dependent variable and hospitalization days was the offset variable. From the model, the incidence rate ratio per year was reported and interpreted as the annual rate increase or decrease. Statistical significance was set at 0.05. All analyses were performed with R version 3.4.1.

Ethical issues

The study was approved by the Ethics Committee at the Bellvitge University Hospital (reference: PR324/15). The need for informed consent was waived by the Clinical Research Ethics Committee.

RESULTS

From January 2003 to December 2016, 227 episodes of PVCR-BSI were identified among hospitalized patients at a university hospital. Mean age: 67y (SD: ±14y), 69% males and median Charlson Score: 3 (interquartile range: 2-5). Characteristics of patients and episodes are summarized in Table II. Median PVC dwell time from insertion to bloodstream infection was 3 days (interquartile range: 2-5) and did not vary significantly over the study period (Figure 1). *S. aureus* was responsible for 115 episodes (50.7%) and mortality of PVCR-BSI was 13.2%.

The PVCR-BSI incidence rates (number of episodes per 10.000 hospital-days) from 2003 to 2016 are shown in Figure 2. After implementing the prevention programme, the incidence rate of PVCR-BSI fell from 30 episodes (1.17 episodes per 10,000 patient-days) in 2003 to eight (0.34 episodes per 10,000 patient-days) in 2016 with a significant rate reduction of 8% per year (rate ratio of 0.92 per year, 95%CI:0.90-0.96). Data on the trends of PVCR-BSI caused by *S. aureus* are shown in Figure 3. The absolute number of episodes due to *S. aureus* fell from 18 episodes in 2003 (0.70 episodes per 10,000 patient-days) to three episodes in 2016 (0.14 episodes/10,000 patients-day) with a significant rate reduction of 9% per year (rate ratio of 0.91 per year, 95%CI:0.86-0.96). Mortality rates over the study period are shown in Figure 4. Mortality significantly decreased from seven episodes (0.27 episodes per 10,000 patients-days) in 2003 to zero in 2016 (figure 4) with a significant rate reduction of 18% per year (rate ratio of 0.82 per year, 95%CI:0.74-0.91.

Compliance with hospital guidelines regarding catheter care in the wards was assessed yearly. Data of catheter care observations performed during round wards are available for the period 2011-2016 and are shown in Table III.

DISCUSSION

The present study sought to determine the impact of a multimodal strategy which included a specific bundle for PVC insertion and maintenance to prevent PVCR-BSI. at our university hospital. These measures were selected according to evidence-based guidelines and on the basis of a rational analysis of the hospital's own data. The implementation of the multimodal strategy during the study period led to a significant reduction in the incidence of PVCR-BSI and associated mortality.

The measures applied included continuous PVCR-BSI surveillance, improvement of PVC insertion and maintenance procedures, educational campaigns targeted at front-line staff, particularly ward nurses, same-day notification of PVCRI-BSIs and assessment of adherence to prevention strategies by periodical ward rounds. The significance of these measures needs to be discussed in detail

As PVCR-BSIs may represent a significant source of hospital-acquired vascular catheter-related bloodstream infections, continuous surveillance is essential to quantify rates of infections and to identify the need for preventive measures; however, this surveillance is still rarely performed for PVC [13]. Although automated electronic surveillance of healthcare-acquired infections is being implemented in many healthcare systems, the accuracy of administrative code data for the detection of vascular catheter-related infections is low [14]. Therefore, in our study trained members of the infection prevention team performed prospective surveillance of PVCR-BSI as described in methods section, even though resources should have been allocated by hospital managers to this task. Although manual surveillance is a potential source of error, to our knowledge there is no best available system for PVCR-BSI surveillance. Furthermore, our hospital is a member of a network of health-care infections surveillance system, the VINCat Programme [15]. Since 2007, more than 50 centres have performed continuous prospective standardized surveillance of PVCR-BSI. Reports from the VINCat programme have shown that the incidence of PVCR-BSI in tertiary and secondary care hospitals is much higher than previously thought [6]. Because catheter-related bloodstream infections are currently considered the most preventable healthcare-associated infections, it seems essential to implement wide surveillance of vascular catheter-related infections, including those caused by PVC [16-18].

Our preventive efforts were also focused on the evidence-based measures listed in Table I. Introduction of 2% alcoholic chlorhexidine for skin antisepsis instead of

povidone iodine and standardization of the use of semi-transparent polyurethane sterile dressing for short peripheral vascular catheter fixation was easily achieved across all hospital wards. Other measures entailing high workload for nurses and incremental costs were implemented after careful revision of our own data and discussion among the infection prevention team members, and with the approval of the Hospital Infection Control Committee. These major changes introduced in 2003 included the use of sterile gloves for catheter insertion and mandatory scheduled replacement of short peripheral catheters within two days for catheters placed in the emergency department and within three days for catheters placed at hospital wards. Regarding the use of gloves, guidelines still recommend the use of the non-touch technique and clean non-sterile gloves for PVC insertion [11]. The reasons for establishing mandatory use of sterile gloves during aseptic insertion in our hospital were multiple; the high incidence rate of PVCR-BSI observed at our hospital and the frequency of the failure to preserve the non-touch technique during catheter insertion observed at our hospital and at others, even after training [19].

The fact that the majority of infections occur within four days of insertion, particularly in catheters placed in the emergency department (where the aseptic conditions may be poor), and the high frequency of *S. aureus,* commonly found in human skin flora, provide convincing evidence of contamination during PVC insertion [9]. Furthermore, the non-sterile gloves available to healthcare workers for catheter insertion are frequently contaminated by environmental organisms including *S. aureus* [20]. For all these reasons, the insertion of PVC into the bloodstream system should be performed observing the highest standard of care, including the use of sterile gloves.

Scheduled replacement of PVC was introduced in our hospital from 2003 to 2013. The resiting of short PVC within 72 hours of placement is still a cause of debate worldwide [3,21,22]. There is no consensus on the optimal time point for PVC change, or whether catheter replacement is required at all, although there is currently an increasing trend towards clinically indicated replacement. No firm recommendations were included regarding scheduled replacement in the current CDC guidelines [11] or in the Cochrane revision [21], although most studies have found that the median dwell time from insertion to bloodstream infection for PVC, particularly for *S. aureus* infections, was four days or more [9]. Randomized studies analysing the risk of bloodstream infections have shown no benefit of replacing PVC every 72h compared to unscheduled replacement [21]. However, these results should be considered with some caution. Although the incidence of PVCR-BSI appears low compared to CVC the absolute

numbers of PVCR-BSI may be high [3]. Catheter replacement within 48 hours for catheters inserted in the emergency department and within 72 hours for catheters inserted in hospital wards was reached in our hospital, according to the data shown in table III. This measure has made a significant contribution to reducing PVCR-BSI rates in our hospital since its implementation.

The hospital policy of scheduled replacement of peripheral catheters inserted in hospital wards changed in 2013, after the introduction of a closed safety peripheral intravenous catheter system in our clinical practice [23]. The material composing the catheter is a determining factor in the development of phlebitis [24] and the introduction of new catheter materials may help to decrease the risk of phlebitis and bloodstream infections. All the currently available information comes from the last decade [25,26] although the risk of adverse events may differ according to the type and design of the peripheral catheters currently available. Since 2013, unscheduled catheter replacement has enabled us to improve patients' well-being, reduce invasive procedures and decrease nurse workload, while preserving the reduction of PCVR-BSI obtained previously.

Finally, educational campaigns explaining the changes were performed in all hospital wards by members of the infection prevention team were introduced early in 2003. It was considered essential to explain the reasons for protocol changes to all front-line professionals. Later, ward rounds were performed regularly to review the implementation of the control measures, followed by a discussion of the problems identified during the rounds. This practice established a crucial interaction between heads of the infection prevention team and healthcare workers on the wards [27]. The immediate feedback of results to ward nursing staff each time a case of PVCR-BSI was detected, with a root-cause analysis, allowed us to raise awareness about the problem and about the need for full implementation of the prevention measures; the attending nursing staff were often unaware of the presence of PVCR-BSI, because the medical team did not systematically inform them of these events.

Our study has some limitations that should be noted. First, it was carried out at a single centre and although the characteristics of PVCR-BSI are similar to those observed in other hospitals, the frequency of infections and the impact of measures may vary. Second, some of the measures applied did not meet the current clinical practice guidelines for PVC management, although they have been considered to be highly effective in our environment. Also, when a variety of prevention measures are applied

simultaneously it is often difficult to identify the ones that are more effective. Among the study's strengths, we highlight the prolonged study period, the high number of cases evaluated and the profound understanding of the problem by the experienced members of the infection prevention team.

In conclusion, PVCR-BSI is a much more common problem in hospitals than previously suspected, and it is associated with high morbidity and mortality rates. The implementation of a multimodal strategy and continuous assessment of performance achieved a sustained reduction in PVCR-BSI, especially in *S. aureus*-associated PVCR-BSI, and had a major impact on mortality.

Competing Interests

The authors have no competing interests to declare.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

[1] Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, et al. National Contact Points for the ECDC pilot point prevalence survey; Hospital Contact Points for the ECDC pilot point prevalence survey. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill. 2012;17. pii: 20316.

[2] Sato A, Nakamura I, Fujita H, Tsukimori A, Kobayashi T, Fukushima S, et al. Peripheral venous catheter-related bloodstream infection is associated with severe complications and potential death: A retrospective observational study. BMC Infect Dis 2017;17. doi:10.1186/s12879-017-2536-0.

[3] Mermel LA. Short-term Peripheral Venous Catheter-Related Bloodstream Infections: A Systematic Review. Clin Infect Dis 2017;65:1757–62. doi:10.1093/cid/cix562.

[4] Zhang L, Cao S, Marsh N, Ray-Barruel G, Flynn J, Larsen E, et al. Infection risks associated with peripheral vascular catheters. J Infect Prev 2016;17:207–13. doi:10.1177/1757177416655472.

[5] Karchmer AW. Bloodstream infections: the problem and the challenge. Int J Antimicrob Agents 2009;34:S2–4. doi:10.1016/S0924-8579(09)70556-4.

[6] Almirante B, Limón E, Freixas N, Gudiol F; VINCat Program. Laboratory-based surveillance of hospital-acquired catheter-related bloodstream infections in Catalonia. Results of the VINCat Program (2007-2010). Enferm Infecc Microbiol Clin. 2012 Jun;30 Suppl 3:13-9. PubMed PMID: 22776149.

[7] Pujol M, Hornero A, Saballs M, Argerich MJ, Verdaguer R, Cisnal M, et al. Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital. J Hosp Infect 2007;67:22–9. doi:10.1016/j.jhin.2007.06.017.

[8] Guembe M, Pérez-Granda MJ, Capdevila JA, Barberán J, Pinilla B, Martín-Rabadán P, et al. Nationwide study on peripheral-venous-catheter- associated-bloodstream infections in internal medicine departments. J Hosp Infect 2017;97:260–6. doi:10.1016/j.jhin.2017.07.008.

[9] Stuart RL, Cameron DRM, Scott C, Kotsanas D, Grayson ML, Korman TM, et al. Peripheral intravenous catheter-associated Staphylococcus aureus bacteraemia: more than 5 years of prospective data from two tertiary health services. Med J Aust 2013;198:551–3.

[10] Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, García D, et al. Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study. J Hosp Infect 2018;99:48–54. doi:10.1016/j.jhin.2017.11.002.

[11] O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO et al. Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52:e162-93. doi: 10.1093/cid/cir257.

[12] O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2002;51(RR-10):1-29.

[13] Zingg W, Sax H, Inan C, Cartier V, Diby M, Clergue F, et al. Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. J Hosp Infect 2009;73:41–6. doi:10.1016/j.jhin.2009.05.015.

[14] Goto M, Ohl ME, Schweizer ML, Perencevich EN. Accuracy of administrative code data for the surveillance of healthcare-associated infections: A systematic review and meta-analysis. Clin Infect Dis 2014;58:688–96. doi:10.1093/cid/cit737.

[15] Gudiol F, Limón E, Fondevilla E, Argimon JM, Almirante B, Pujol M. The development and successful implementation of the VINCat Program. Enferm Infecc Microbiol Clin 2012;30:3–6. doi:10.1016/S0213-005X(12)70089-7.

[16] Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the Proportion of Healthcare-Associated Infections That Are Reasonably Preventable and the Related Mortality and Costs. Infect Control Hosp Epidemiol 2011;32:101–14. doi:10.1086/657912.

[17] Van Mourik MSM, Perencevich EN, Gastmeier P, Bonten MJM. Designing Surveillance of Healthcare-Associated Infections in the Era of Automation and Reporting Mandates. Clin Infect Dis 2018;66:970–6. doi:10.1093/cid/cix835.

[18] Mitchell BG, Russo PL. Preventing healthcare-associated infections: the role of surveillance. Nurs Stand 2015;29:52–8. doi:10.7748/ns.29.23.52.e9609.

[19] Fakih MG, Jones K, Rey JE, Takla R, Szpunar S, Brown K, et al. Peripheral venous catheter care in the emergency department: Education and feedback lead to marked improvements. Am J Infect Control 2013;41:531–6. doi:10.1016/j.ajic.2012.07.010.

[20] Hughes KA, Cornwall J, Theis JC, Brooks HJL. Bacterial contamination of unused, disposable non-sterile gloves on a hospital orthopaedic ward. Australas Med J 2013;6:331–8. doi:10.4066/AMJ.2013.1675.

[21] Webster J, Osborne S, Rickard CM, New K. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. Cochrane Database Syst Rev 2015;8:CD007798. doi:10.1002/14651858.CD007798.pub4.

[22] Safdar N, McKinley LM, Davidson B, Broome C, Schenk J. Recommendations to replace peripheral venous catheters every 72-96 hours: Is a single reference enough? J Hosp Infect 2011;79:172–3. doi:10.1016/j.jhin.2011.06.005.

[23] González López JL, Arribi Vilela A, Fernández del Palacio E, Olivares Corral J, Benedicto Martí C, Herrera Portal P. Indwell times, complications and costs of open vs closed safety peripheral intravenous catheters: A randomized study. J Hosp Infect 2014;86:117–26. doi:10.1016/j.jhin.2013.10.008.

[24] Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters: A randomized controlled trial. Ann. Intern. Med., vol. 114, 1991, p. 845–54. doi:10.7326/0003-4819-114-10-845.

[25] Jacquot C, Fauvage B, Bru JP, Croize J, Calop J. Peripheral venous catheterization: influence of catheter composition on the occurrence of thrombophlebitis. Ann Fr Anesth Reanim. 1989;8:620-4. French. PubMed PMID: 2633660.

[26] Karadağ a, Görgülü S. Effect of two different short peripheral catheter materials on phlebitis development. J Intraven Nurs 2000;23:158–66.

[27] Knobloch MJ, Chewning B, Musuuza J, Rees S, Green C, Patterson E, Safdar N. Leadership rounds to reduce health care-associated infections. Am J Infect Control. 2018;46:303-310. doi: 10.1016/j.ajic.2017.08.045.

Table I: Measures applied for prevention of PVCR-BSI during the study period

PERIOD	INFECTION CONTROL INTERVENTION		LEVEL OF EVIDENCE (a)
2003-2005	Continuous surveillance of PVCR-BSI	Daily meetings with microbiology team	IA
		Review of the episodes of PVCR-BSI found	IA
	Implementation of the bundle of measures	Introduction of sterile gloves	Unresolved issue
		Reinforcement of aseptic care technique	IB
		Schedule replacement of peripheral catheters	Unresolved issue
		Skin antisepsis with alcohol base (70%) solution of chlorhexidine gluconate (0.5%)	IA
		Extension tube	Unresolved issue
		Semi-permeable transparent dressings for catheter sites	IA
	Healthcare worker training	Regular meetings and training sessions for healthcare workers	IA
		Review of the hospital guidelines for prevention of PVCR-BSI	IA
		Pocket card guidelines for hospital staff	IB
		Wall charts of guidelines for the insertion of peripheral vascular catheters	IB
	Feedback system	Notifications to ward staff and discussion with the ward nursing team after each case of PVCR-BSI	III
	Upgrade skin antisepsis	Skin antisepsis with alcohol base (70%) or solution of chlorhexidine	IA

		gluconate (2%)	
2006-2009	Flushing	Introduction of pre-filled syringes	IV
2010-2016	Upgrade the type and the guidelines for the catheters in use	Introduction of closed IV catheter system	IC
		Unscheduled replacement	IB

(a) According to 2011 CDC guidelines, reference [11].

Table II: Clinical epidemiology, microbiology and outcomes of PVCR-BSI

Variables	2003-2005 N=71	2006-2009 N=78	2010-2016 N=78	Overall N=227
Male	44 (62%)	55 (70.5%)	57 (73.1%)	156 (68.7%)
Age >65	38 (53.5%)	58 (74.4%)	51 (65.4%)	147 (64.8%)
Area				
Medical	51 (71.8%)	35 (44.9%)	38 (48.7%)	124 (54.6%)
Surgery	20 (28.2%)	43 (55.1%)	40 (51.3%)	103 (45.4%)
Median dwell time from insertion to BSI (IQR) (a)	4 (3-6)	4 (3-7)	5 (3-6)	4 (3-6)
Microorganisms				
Gram-positive	63 (88.7%)	55 (70.5%)	55 (70.5%)	173 (76.2%)
Gram-negative bacilli	9 (12.7%)	22 (28.8%)	21 (26.9%)	52 (22.9%)
Staphylococcus aureus	41(57.7%)	39 (50%)	35 (44.9%)	115 (50.7%)
MSSA (b)	34 (47.9%)	36 (46.6%)	28 (35.9%)	98 (43.2%)
MRSA (c)	7 (9.9%)	3 (3.8%)	7 (9%)	17 (7.5%)
Coagulase-negative staphylococci	22 (31%)	15 (19.2%)	19 (24.4%)	56 (24.7%)
Enterococcus spp.	0%	1 (1.3%)	1 (1.3%)	2 (0.9%)
Acinetobacter baumannii	0%	3 (3.8%)	1 (1.3%)	4 (1.8%)
Pseudomonas aeruginosa	0%	1 (1.3%)	2 (2.6%)	3 (1.3%)
Candida spp.	0%	1 (1.3%)	0%	1 (0.4%)
Charlson > 4	45 (63.4%)	32 (41%)	33 (42.3%)	100 (48.5%)
30 days mortality (episodes)/10,000 patient-days	15 (21.1%)	10 (12.8%)	5 (6.4%)	30 (13.21%)

(a) IQR: Interquartile range
(b) Methicillin susceptible *S. aureus*

Table III: Assessment of catheter care performance during hospital round wards

	2011 (n=492)	2012 (n=490)	2013 (n=487)	2014 (n=495)	2015 (n=485)	2016 (n=669)
ED Placement (a)	13.2%	12.6%	13.9%	12.7%	10.5%	9.5%
48h Replacement (b)	86.1%	88.7%	94.1%	98.4%	96.0%	96.8%
HW Placement (c)	86.7%	87.3%	86.0%	87.2%	89.4%	90.4%
72h Replacement (d)	95.3%	94.8%	97.6%	97.2%	96.31%	99.6%
Appropriate dressing	96.5%	97.3%	98.3%	97.1%	98.1%	98.6%
Appropriate insertion catheter site	95.5%	95.5%	96.5%	96.1%	97.7%	97.9%
Presence of extension tube	95.9%	96.5%	96.7%	97.3%	98.7%	97.9%
Absence of phlebitis	99.3%	99.5%	99.7%	99.3%	99.7%	99.5%
Absence of extravasation	99.3%	99.7%	100%	100%	100%	100%
Clinical chart registration	98.1%	98.5%	98.7%	98.9%	98.7%	99.8%
TOTAL	95.8%	96.3%	97.7%	98.0%	98.1%	98.7%

(a) % of PVC placed at the emergency ward
(b) % of PVC placed at the emergency wards and replaced within 48 hours according to hospital guidelines
(c) % of PVC placed at hospital wards/operating room
(d) % of PVC placed at the hospital wards/operating room and replaced within 72 hours according to hospital guidelines

Figure 1: Median well time of vascular catheterization amog patients

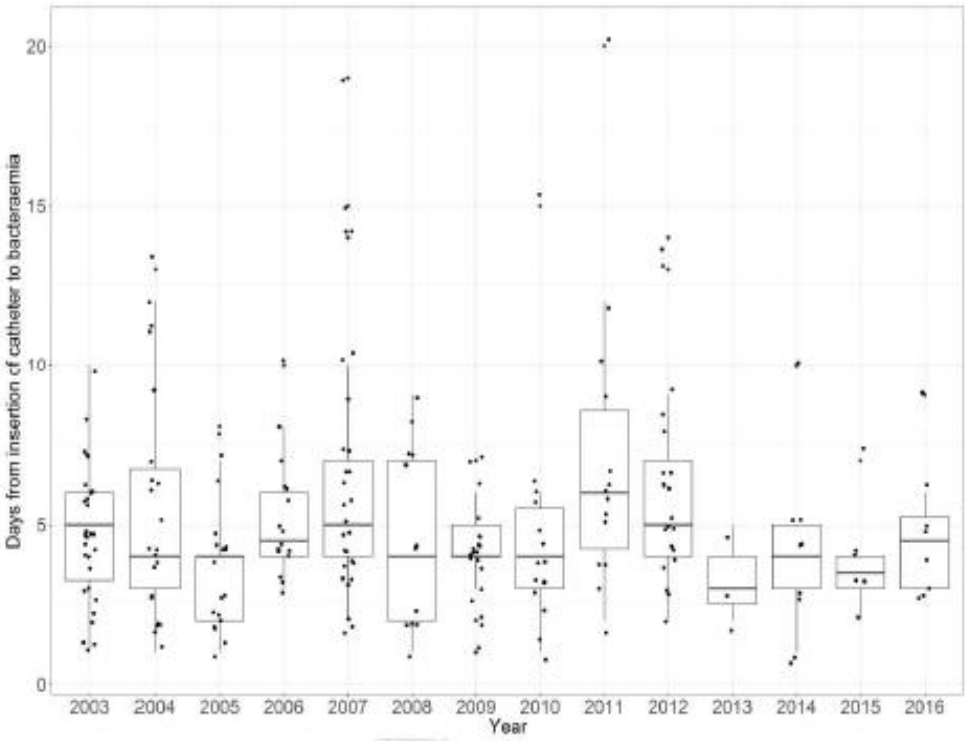


Figure 2: Episodes of PVCR-BSI and rate per 10,000 hospitalizations from 2003 to 2016.

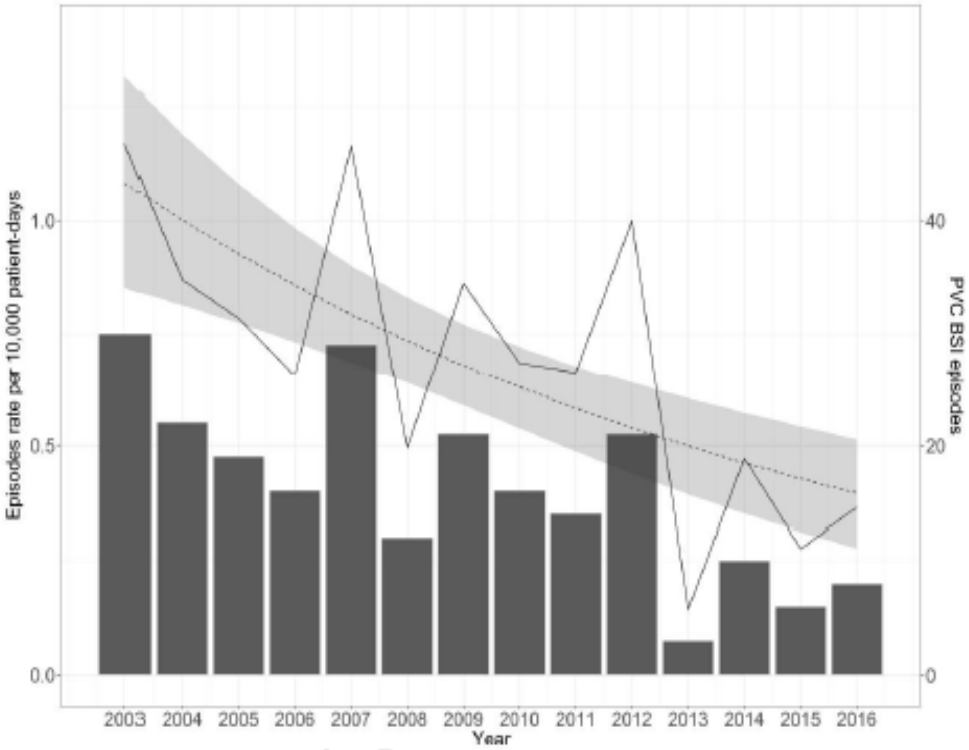


Figure 3: Episodes of PVCR-BSI caused by *Staphylococcus aureus* and rates per 10,000 hospitalizations from 2003 to 2016.

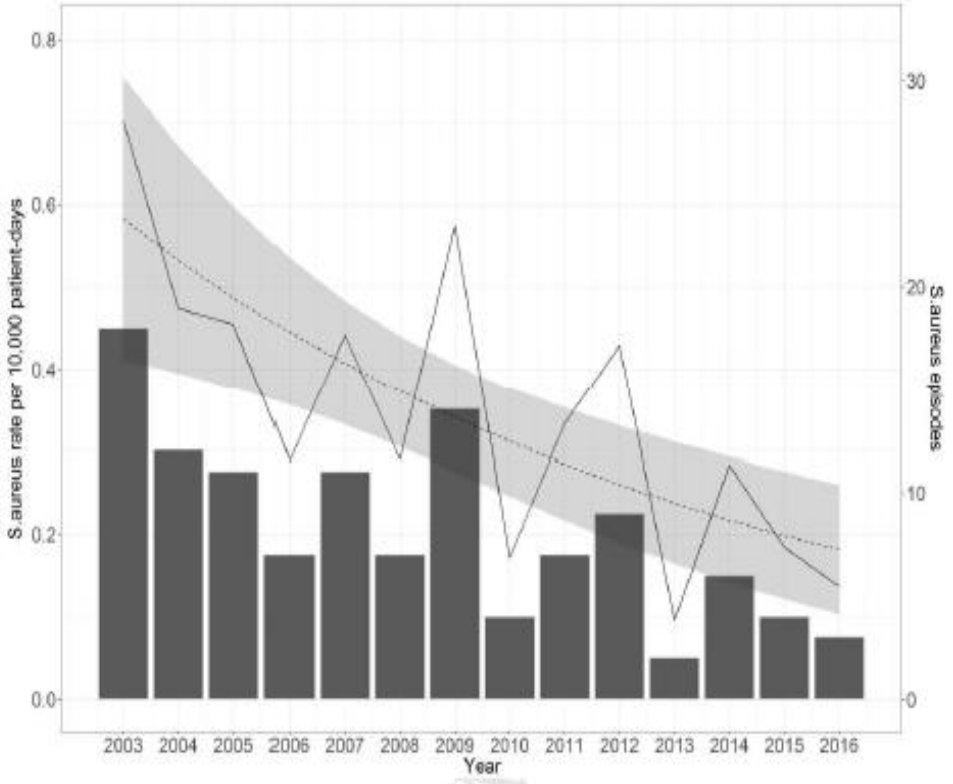


Figure 4: Mortality associated to PVCR-BSI and rates per 10,000 hospitalizations from 2003 to 2016

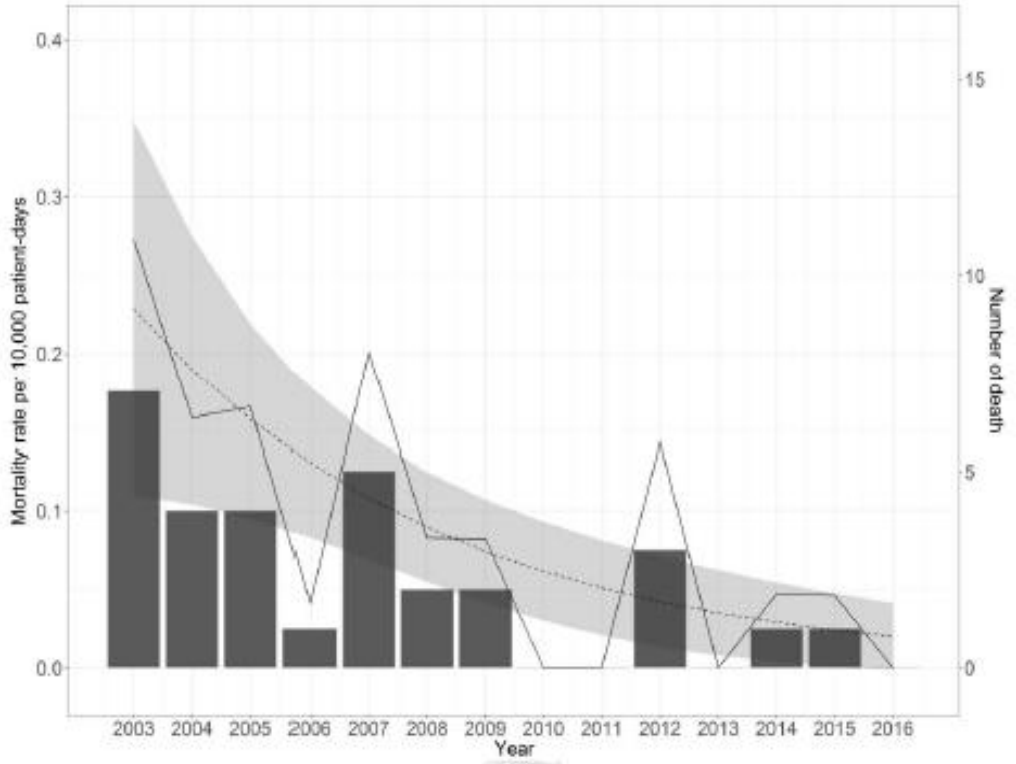


Figure legends

Figure 1
Box plots of days from insertion of catheter to bacteraemia are presented per years; each dot is patient days from insertion of catheter to bacteraemia.

Figure 2
Bars are the number of observed PVCR- BSI episodes, solid line is PVCR- BSI rate per 10,000 patient-days, dashed line is predicted PVCR- BSI rate per 10,000 patient-days by Poisson regression model, and shaded area is 95% confidence interval on prediction.

Figure 3
Bars are the number of observed *S.aureus* episodes, solid line is *S.aureus* rate per 10,000 patient-days, dashed line is predicted *S.aureus* rate per 10,000 patient-days by Poisson regression model, and shaded area is 95% confidence interval on prediction.

Figure 4
Bars are the number of deaths among patients with PVCR-BSI, solid line is mortality rate per 10,000 patient-days, dashed line is predicted mortality rate per 10,000 patient-days by Poisson regression model, and shaded area is 95% confidence interval on prediction.

Annex II

Journal of Hospital Infection 99 (2018) 48–54

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study

P. Saliba [a,c], A. Hornero [a], G. Cuervo [a], I. Grau [a], E. Jimenez [a], D. García [b], F. Tubau [b,d], J.M. Martínez-Sánchez [c], J. Carratalà [a], M. Pujol [a,*]

[a] Department of Infectious Diseases, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), University of Barcelona, Barcelona, Spain
[b] Department of Microbiology, Hospital Universitari de Bellvitge, Barcelona, Spain
[c] Universitat Internacional de Catalunya, Barcelona, Spain
[d] CIBER de Enfermedades Respiratorias, ISCIII, Madrid, Spain

ARTICLE INFO

Article history:
Received 18 September 2017
Accepted 3 November 2017
Available online 8 November 2017

Keywords:
Catheter-related bloodstream infections
Risk factors for mortality
Staphylococcus aureus bloodstream infections

SUMMARY

Background: Vascular catheter-related bloodstream infections (CRBSIs) are highly preventable hospital-acquired infections and a major threat to patient safety. While there is significant information regarding CRBSI outcome among intensive care unit (ICU) patients, data regarding non-ICU patients are scarce.

Aim: To determine the risk factors associated with 30-day mortality among non-ICU patients with nosocomial CRBSIs.

Methods: Prospective cohort study of non-ICU patients with nosocomial CRBSIs in a tertiary care centre between January 2004 and December 2014. The primary outcome was 30-day mortality, defined as death from any cause within 30 days of CRBSI. Follow-up was performed 30 days after CRBSI onset. Time until death was the dependent variable in Cox regression analysis.

Findings: In total, 546 cases of CRBSI were identified. The mean age of patients was 64.5 years [interquartile range (IQR) 55–75 years], 66% were male, and the mean Charlson score was 3.59 (IQR 2–5). Of the 546 cases, 58.4% resulted from central venous catheters and 41.6% from peripheral venous catheters. The causative agents were Gram-positive cocci (70.1% of cases), Gram-negative bacilli (31.1%) and *Candida* spp. (1%). Mortality within 30 days was 13.9%, with no significant changes over the study period. Independent risk factors for 30-day mortality were Charlson score ≥4 [hazard ratio (HR) 1.80, 95% confidence interval (CI) 1.19–2.73], *Staphylococcus aureus* infection (HR 2.67, 95% CI 1.61–4.43) and *Candida* spp. infection (HR 6.1, 95% CI 2.08–18.04). Age; area of admission; type, use and site of vascular catheter; and administration of appropriate empirical antibiotic treatment were not independent risk factors for 30-day mortality.

* Corresponding author. Address: Infectious Diseases Department, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Tel.: +34 933357011; fax: +34 932607637.
E-mail address: mpujol@bellvitgehospital.cat (M. Pujol).

https://doi.org/10.1016/j.jhin.2017.11.002

Conclusion: Nosocomial CRBSIs outside ICUs are associated with high risk of mortality, particularly among patients with a higher Charlson score and bloodstream infections caused by *Staphylococcus aureus* and *Candida* spp.

Introduction

Vascular catheters are the most commonly used medical devices in hospitals. According to a large European prevalence study, a vascular catheter was present in almost 55% of hospitalized patients [1]. Almost all of the patients required one or more vascular catheters during hospitalization for therapeutic support, haemodynamic monitoring or diagnostic procedures. In non-intensive care units (non-ICUs), vascular catheter utilization, measured as the ratio of device-days to patient-days, is lower than in ICUs, but the total burden of catheters in use is higher in the non-ICU setting [2].

Adverse events related to vascular catheterization are common. Catheter-related bloodstream infections (CRBSIs) are among the most serious complications, causing high morbidity, high mortality and a rise in hospital costs [3]. The incidence of CRBSIs varies according to vascular catheter type, characteristics and insertion site [4]. Consequently, CRBSI rates are higher for central venous catheters (CVCs) than for peripheral venous catheters (PVCs), although the high number of patients exposed to PVCs means that the absolute number of PVC BSIs could be substantial [5–7].

CRBSIs are the most preventable cause of healthcare-related infections [8]. Over the last decade, the implementation of interventions to prevent CRBSIs has led to a significant and sustained reduction in the incidence of infection, particularly in ICUs, but also in non-ICU settings [9–11]. However, most studies have focused on the epidemiology and outcomes of CRBSIs in the ICU setting, and scarce information is available regarding non-ICU settings. Identifying risk factors associated with CRBSI mortality is relevant to improving patient outcomes. The aim of this study was to determine the risk factors associated with 30-day mortality among patients with nosocomial CRBSIs on non-ICU wards.

Methods

Study design, setting and population

A prospective cohort study was conducted at Bellvitge University Hospital, a 700-bed tertiary care teaching hospital for adults in Barcelona, Spain. Each year, an average of 28,000 patients are admitted (approximately 340,000 patient-days). The primary outcome was 30-day crude mortality among non-ICU patients with nosocomial CRBSIs. The inclusion criteria were: consecutive episodes of nosocomial CRBSIs diagnosed during admission to medical and surgical wards between January 2004 and December 2014. Exclusion criteria were: episodes of CRBSI diagnosed during ICU hospitalization or during outpatient care.

Data collection

Episodes of bacteraemia were reported daily from the microbiology laboratory to the infection control team. Patients were examined on the wards, and those who met the criteria for nosocomial CRBSI were followed-up for 30 days from the onset of bacteraemia and included in a standardized protocol. The following data were collected: age, sex, Charlson score, area of admission, type of catheter, purpose of use, days of insertion, aetiology, and empirical antibiotic treatment. This study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations for reporting cohort studies [12].

Definitions

Nosocomial CRBSI was diagnosed in any patient with clinical signs and symptoms of sepsis according to the definition of the Infectious Diseases Society of America when a growth of concordant bacterial species in a semi-quantitative tip culture and blood culture was observed, without another obvious source of bacteraemia [13]. In the absence of a catheter tip culture, the diagnosis of CRBSI required either: (i) phlebitis; or (ii) clear resolution of clinical symptoms after catheter withdrawal, and careful exclusion of an alternative explanation for bacteraemia. For common skin micro-organisms such as coagulase-negative staphylococci, at least two consecutive blood cultures were required with the same species and identical susceptibility pattern to indicate possible CRBSI.

Co-morbidity was measured using the Charlson score, as described elsewhere [14]. The Charlson score was dichotomized for the purpose of the analysis into two categories: <4 and ≥ 4. Days since insertion was defined as the dwelling time from catheter insertion until removal, and was dichotomized into <4 and ≥ 4 days. Empirical antibiotic treatment was defined as antibiotics administered within 48 h of the date on which the first positive blood culture was drawn, and was considered appropriate if the strain was susceptible to at least one of the antibiotics administered. Mortality was defined dichotomously as death occurring from any cause within 30 days of onset of CRBSI. Patients who remained in hospital after 30 days of CRBSI were counted as alive. Attributable mortality was not recorded to avoid subjectivity in determining cause of death.

Microbiological identification and susceptibility testing

Two sets of two blood samples were collected from patients with a suspected bloodstream infection. The blood samples were processed using a BACTEC 9240 system (Becton–Dickinson Microbiology Systems, Franklin Lakes, NJ, USA), with an incubation period of five days at 35°C before being discharged. If bacteria were observed after microscopic Gram stain examination, blood bottles were subcultured on to Chocolate agar plates. Catheter tips were cultured after removal, as described elsewhere [15]. The tip was rolled three to four times on a blood agar plate, which was incubated at 37°C for 48 h and then

analysed. The presence of ≥15 colony-forming units was considered as evidence of local catheter infection.

Statistical analysis

Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Qualitative and stratified continuous variables were compared using Fisher's exact test or Pearson's Chi-squared test. Relative risks were calculated with 95% confidence intervals (CI) in univariate analysis. Time (days) until death was the dependent variable in the Cox regression analysis, and was surveyed for 30 days after the onset of bacteraemia. Only those variables that were statistically significant ($P < 0.05$) in the univariate analysis were included in the model. A forward stepwise procedure was used in the Cox regression analysis. The Chi-squared test for trend in proportions was performed to determine significant variations in mortality during the study period. For variables significantly associated with mortality, a Kaplan–Meier curve was plotted to show the survival probabilities at 30 days. All analyses were performed using SPSS Version 15 (IBM Corp., Armonk, NY, USA).

Ethical issues

The study was approved by the Ethics Committee at Bellvitge University Hospital (Reference PR324/15). Informed consent was waived by the Clinical Research Ethics Committee.

Results

During the study period, 546 episodes of CRBSI were diagnosed in 537 non-ICU patients. The CRBSI rate was 0.23/1000 patient-days. Thirty-day mortality was 13.9% (76 of 546 episodes) and did not vary significantly during the study period (Figure 1). Mortality varied according to co-morbidities, type of ward, type of catheter, insertion site and aetiology (Table I). Univariate and multi-variate analyses of risk factors associated

Table I
Mortality according to patient characteristics, hospital ward, catheter type, place of insertion and aetiology

	Mortality *N* (%)
Age ≥65 years (*N* = 306)	51 (16,7)
Charlson score ≥4 (*N* = 244)	51 (20.9)
Type of ward	
Medical (*N* = 249)	45 (18.1)
Surgical (*N* = 297)	31 (10.4)
Peripheral venous catheter	
Short-line (*N* = 141)	20 (14.9)
Midline (*N* = 63)	6 (9.5%)
Central venous catheter	
Subclavian (*N* = 105)	15 (14.3)
Jugular (*N* = 97)	13 (13.4)
Femoral (*N* = 64)	12 (18.8)
PICC (*N* = 53)	9 (17)
Use of catheter	
Medication, fluids (*N* = 351)	51 (14.5)
Haemodialysis (*N* = 80)	15 (18.8)
Parenteral nutrition (*N* = 115)	10 (8.7%)
Aetiology	
Gram-positive bacteria (383)	32 (16.2)
Staphylococcus aureus (*N* = 212)	49 (23.1)
MSSA (*N* = 171)	34 (19.9)
MRSA (*N* = 41)	15 (36.6)
Coagulase-negative staphylococci (*N* = 150)	8 (5.3)
Enterococci (*N* = 25)	5 (20)
Gram-negative bacilli (*N* = 170)	16 (9.4)
Klebsiella pneumoniae (*N* = 42)	2 (4.8)
Pseudomonas aeruginosa (*N* = 38)	7 (18.4)
Acinetobacter baumannii (*N* = 10)	10 (0)
Candida spp. (*N* = 7)	4 (57.1)

PICC, peripheral inserted central venous catheter; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*.

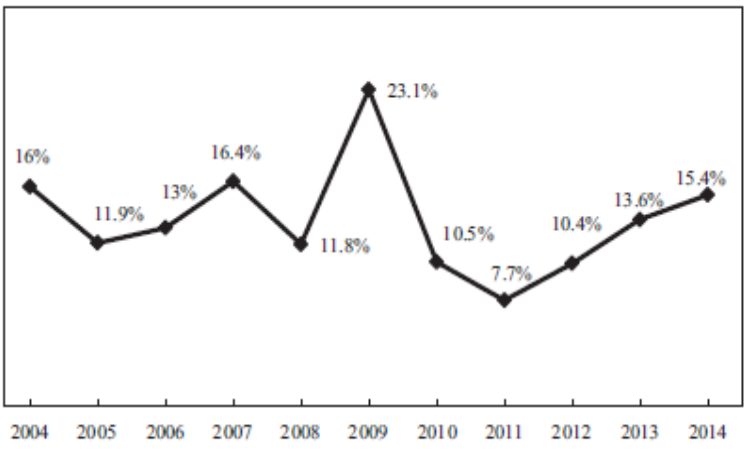


Figure 1. Yearly mortality rate among patients with catheter-related bloodstream infections (2004–2014).

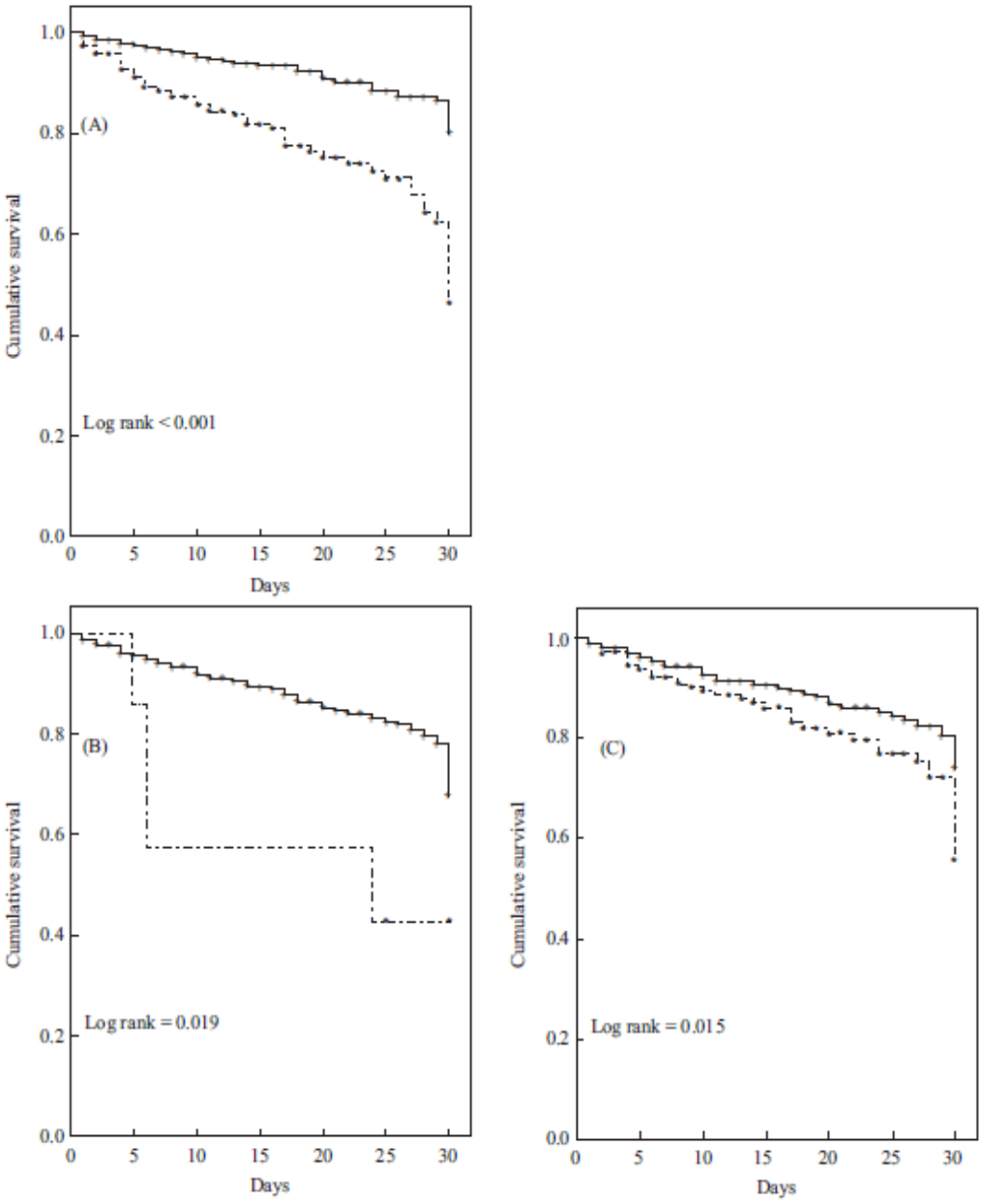


Figure 2. Kaplan–Meier survival curves for (A) *Staphylococcus aureus*, (B) *Candida* spp. and (C) Charlson score ≥4.

had a 2.27-fold higher risk of mortality than patients without CRBSIs after controlling for other hospital-acquired infections, APACHE II score and the presence of multiple catheters. Similarly, a meta-analysis including 18 studies and 1976 episodes of CRBSI found a 2.75-fold higher risk of mortality among patients with CVC BSIs [19]. These figures, combined with the present results, show clearly that CRBSIs outside ICUs remain a major problem that may have a negative effect on patient outcomes.

Little is known about the factors contributing to CRBSI mortality in non-ICU patients, as few studies have addressed this issue. Cox regression analysis identified a Charlson score ≥4, *S. aureus* infection and *Candida* spp. infection as independent associated factors for CRBSI mortality, while type of catheter, insertion site and appropriate empirical antibiotic therapy were not independent predictive factors. The Charlson score was developed as a prognostic index to predict one-year mortality among patients admitted to acute care hospitals

[20]. Multi-variate analysis showed that a Charlson score ≥4 was an independent risk factor for mortality among non-ICU patients with CRBSIs, and that the mortality rate in this population was as high as 43%.

It is predictable that patients with higher Charlson scores have higher risk of mortality. However, it was difficult to interpret mortality related to Charlson score because it was not possible to discriminate mortality due to severity of underlying disease from mortality due to CRBSIs because the cohort of patients did not include patients without CRBSIs. Nevertheless, these results suggest that the consequences of CRBSI in patients with high Charlson scores are more serious than in patients with low Charlson scores, and can certainly lead to early mortality.

S. aureus was identified as the micro-organism most frequently associated with increased mortality, approaching 23%. This figure correlates with studies reporting the association between catheter-associated *S. aureus* bacteraemia and mortality rates ranging from 15% to 20% [21]. Moreover, a number of studies have examined the association between short peripheral vascular catheters and bacteraemia caused by *S. aureus*, reporting a high mortality rate due to this complication [5,22,23].

This study only identified seven CRBSI cases caused by *Candida* spp. and the mortality rate was as high as 57%, making these yeast species one of the main independent risk factors for mortality. However, due to the small sample size of *Candida* spp., interpretation of the data, particularly regarding the broad 95% CI of HR, should be made with caution. Catheter-associated BSIs caused by *Candida* spp. are more common among ICU patients, with reported rates varying between 36% and 61% [24,25]. In the present study, the rate of CRBSIs due to *Candida* spp. was 1% among non-ICU patients, which is lower than that reported previously. Sustained low rates of catheter-related candidaemia in the study hospital could be attributed to antimicrobial stewardship policies. In contrast with the aetiologies discussed above, coagulase-negative staphylococci were associated with a low mortality rate of 5.3%; this finding could be explained by the low intrinsic virulence of this group of organisms [26].

Interestingly, none of the following factors were found to be associated with increased mortality: type of catheter, central vs peripheral catheters, insertion site, and administration of inadequate empirical antibiotic therapy.

Although this prospective study involved a large population over a prolonged period, there are a number of limitations that should be acknowledged. First, the study was performed at a single hospital; therefore, the generalizability of the results should be approached with caution. In addition to patient characteristics, the frequency of catheter use and *S. aureus* infections may differ from those observed in other facilities, and these factors could account for the results observed in this study. Furthermore, early removal of the vascular catheter and the presence of septic shock, two additional factors with a potential impact on outcomes, were not analysed in this study.

To conclude, nosocomial CRBSIs outside ICUs carry a high risk of mortality, particularly among patients with a higher Charlson score and CRBSIs caused by *S. aureus* and Candida spp. The results of this study highlight the importance of implementing programmes for the control of CRBSIs in non-ICU patients, as for ICU patients, and could lead to a significant reduction in CRBSI mortality.

Acknowledgements

The authors wish to thank the Department of Microbiology of Bellvitge University Hospital (MA Dominguez) for study support.

Conflict of interest statement
None declared.

Funding sources
None.

References

[1] Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, et al. National contact points for the ECDC pilot point prevalence survey, hospital contact points for the ECDC pilot point prevalence survey. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill 2012;17: pii=20316.

[2] Kallen AJ, Patel PR, O'Grady NP. Preventing catheter-related bloodstream infections outside the intensive care unit: expanding prevention to new settings. Clin Infect Dis 2010;51:335–41.

[3] Stevens V, Geiger K, Concannon C, Nelson RE, Brown J, Dumyati G, et al. Inpatient costs, mortality and 30-day re-admission in patients with central-line-associated bloodstream infections. Clin Microbiol Infect 2014;20:O318–24.

[4] Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 2006;81:1159–71.

[5] Pujol M, Hornero A, Saballs M, Argerich MJ, Verdaguer R, Cisnal M, et al. Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital. J Hosp Infect 2007;67:22–9.

[6] Zingg W, Sax H, Inan C, Cartier V, Diby M, Clergue F, et al. Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. J Hosp Infect 2009;73:41–6.

[7] Almirante B, Limón E, Freixas N, Gudiol F. VINCat Program. Laboratory-based surveillance of hospital-acquired catheter-related bloodstream infections in Catalonia. Results of the VINCat Program (2007–2010). Enferm Infecc Microbiol Clin 2012;30(Suppl. 3):13–9.

[8] Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect 2003;54:258–66.

[9] Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355:2725–32.

[10] Freixas N, Bella F, Limón E, Pujol M, Almirante B, Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: a multicentre study. Clin Microbiol Infect 2013;19:838–44.

[11] García-Rodríguez JF, Álvarez-Díaz H, Vilariño-Maneiro L, Lorenzo-García MV, Cantón-Blanco A, Ordoñez-Barrosa P, et al. Epidemiology and impact of a multifaceted approach in controlling central venous catheter associated blood stream infections outside the intensive care unit. BMC Infect Dis 2013;13:445.

[12] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:1623–7.

[13] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by

the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1–45.
[14] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.
[15] Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977;296:1305–9.
[16] Zingg W, Pittet D. Peripheral venous catheters: an underevaluated problem. Int J Antimicrob Agents 2009;34:S38–42.
[17] Stuart RL, Cameron DR, Scott C, Kotsanas D, Grayson ML, Korman TM, et al. Peripheral intravenous catheter-associated *Staphylococcus aureus* bacteraemia: more than 5 years of prospective data from two tertiary health services. Med J Aust 2013;198:551–3.
[18] Rhee Y, Heung M, Chen B, Chenoweth CE. Central line-associated bloodstream infections in non-ICU inpatient wards: a 2-year analysis. Infect Control Hosp Epidemiol 2015;36:424–30.
[19] Ziegler MJ, Pellegrini DC, Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. Infection 2015;43:29–36.
[20] Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749–59.
[21] Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GR, et al. Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009;191:368–73.
[22] Mermel LA. Short-term peripheral venous catheter-related bloodstream infections: a systematic review. Clin Infect Dis 2017;10:1757–62.
[23] Sato A, Nakamura I, Fujita H, Tsukimori A, Kobayashi T, Fukushima S, et al. Peripheral venous catheter-related bloodstream infection is associated with severe complications and potential death: a retrospective observational study. BMC Infect Dis 2017;17:434.
[24] Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, et al. Epidemiology, management, and risk factors for death of invasive candida infections in critical care: a multicenter, prospective, observational study in France (2005–2006). Crit Care Med 2009;37:1612–8.
[25] Kett DH, Azoulay E, Echeverria PM, Vincent JL. Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. Candida bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med 2011;39:665–70.
[26] Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. Clin Microbiol Rev 2014;27:870–926.

Annex III

The impact of pre-filled saline flush syringes in reducing the incidence of peripheral venous catheter failure. A quasi-experimental multicenter study

Saliba P1, Hornero A1, de Carli G2, Marani A2, Lopez AF 3, Iftimie S 3, Castro A, 3 Diaz-Brito V 4, Jimenez C 4, Martinez JM5, Jimenez E1, Carratala J1, Pujol M1
1Department of infectious diseases,Hospital Universitari de Bellvitge. 2Department of epidemiology and reasearch, Lazzaro Spallanzani Hospital. 3Department of Internal Medicine, Hospital Universitari Sant Joan de Reus. 4Department of Internal Medicine, Parc Sanitari Sant Joan de Déu. 5Department of basic sciences, Universitat Internacional de Catalunya

Email: patrickuic@uic.es **Nº 147**

BACKGROUND

The unscheduled replacement of peripheral venous catheter (PVC) is common and frequently entails a new invasive procedure. Flushing the catheter before and after use, maintains patency and could prolong catheter dwell time. Although saline flushing is highly recommended, compliance in the daily routine care is uncertain.

OBJECTIVE

To determine whether there are significant differences in overall PVC failure rates before and after introduction of pre-filled flushing syringes and to assess risk factors for PVC failure.

METHODS

Methods: quasi-experimental design; before-and-after intervention study.
Intervention: Introduction of pre-filled saline syringes for flushing. Multicenter study conducted in medical and surgical units in 3 European hospitals for a period of 9 months (5 months pre-intervention, 4 months intervention).
Main outcome: Catheter failure, defined as a composite variable encompassing unscheduled withdrawal or replacement of PVC because of any of the following conditions: phlebitis, thrombosis extravasation, suspected infection.
Statistical analysis: A multivariate Cox proportional hazard ratio was used to identify factors associated with the occurrence of PVC failure.

RESULTS

Data were analysed for 3,853 PVCs in 1,915 patients. Overall, the incidence of **PVC failure was 50.1%,** mainly due to phlebitis and infiltration/extravasation. Compared to pre-intervention period, a significant decrease in PVC failure rate was observed in the intervention period (55.4% vs 44.8%, p<0.01). **Risk factors for PVC failure** were: **Charlson score ≥4** (HR:1.64;95%CI:1.069-2.527), **days of hospital stay ≥10** (HR:1.46;95%CI:1.172-1.837), and the **use of PVC "Type D"** (HR:1.75;95%CI:1.05-2.91), while **intervention period** (HR:0.76;95%CI:0.63-0.91) and **insertion of PVC at traumatology ward** (HR:0.43;95%CI:0.21-0.85) **reduced the risk of PVC failure** (Table 1).
Figure 1, shows dwell time of PVC among the period 1 and 2. By the 5th day of catheterization, only 40% of PVC in the period 1 survive without a failure, while 60% of PVC survive without any failure in the period 2.

	Non Catheter Failure N=1906	Catheter failure N=1947	P Value	Hazard ratio	CI 95%
Age ≥ 65	1176 (61.7%)	1190 (61.1%)	0.716		
Gender (Male)	1071 (56.2%)	1116 (57.3%)	0.495		
Charlson score ≥4	871 (45.7%)	1097 (56.3%)	0.000	1.644	1.069-2.527
Days of hosp ≥ 10	713 (37.4%)	1289 (66.2%)	0.000	1.468	1.172-1.837
Days of cath≥ 4	993 (52.1%)	712 (36.6%)	0.000		
Unit of Hospitalisation					
trauma	324 (17%)	86 (4.4%)	0.000	0.431	0.219-0.851
Type of catheter					
Catheter A	1587 (83.3%)	1475 (75.8%)	0.000		
Catheter B	129 (6.8%)	104 (5.3%)	0.037		
Catheter C	33 (1.7%)	75 (3.9%)	0.000		
Catheter D	157 (8.2%)	293 (15%)	0.000	1.75	1.05-2.91
Unit of catheterisation					
Hospital	1118 (58.7%)	1181 (60.7%)	0.212		
Emergency Unit	599 (31.4%)	661 (33.9%)	0.051		
Others	189 (9.9%)	105 (5.4%)	0.000		
Charlson score ≥4	871 (45.7%)	1097 (56.3%)	0.000	1.644	1.069-2.527
Intervention period	974 (51.1%)	791 (40.6%)	0.000	0.761	0.630-0.919

Table 1: Univariate and multivariate analysis of the risk factors associated with PVC failure

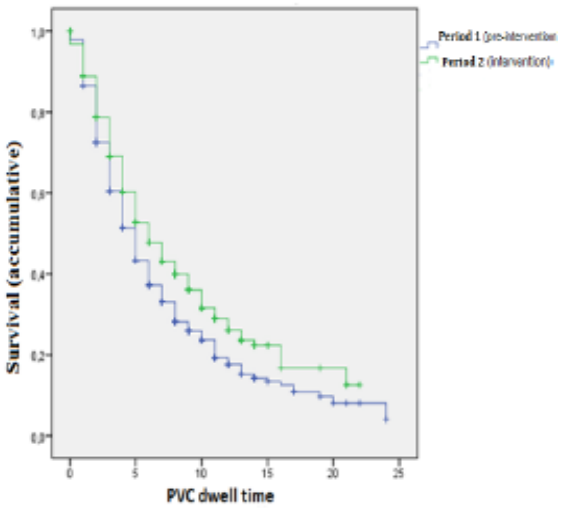


Figure 1:Kaplan meier curve showing the difference in the PVC dwell time between Period 1 and 2 .

CONCLUSIONS

We found that unscheduled PVC replacement was very high in study hospitals. The risk of catheter failure varied according to patient comorbidities, days of hospital stay, and type of PVC. The introduction of catheter flushing with pre-filled saline syringes had a significant impact on reducing unscheduled vascular catheter replacement.

Annex IV

A complementary tool to validate surgical site infection surveillance data (VINCat Program, Catalonia, Spain).

E. Limón[1], P. Saliba[1], J. Lopez-Contreras[1,3], F. Gudiol[1], and M. Pujol[1,2], on behalf of VINCat group.
[1] VINCat Programme, Departament de Salut Catalonia, Spain. [2]Hospital Universitari de Bellvitge. [3]Hospital de la Santa Creu i Sant Pau

vincat@gencat.cat

№ 007

BACKGROUND

Validation is considered an essential issue in order to establish data consistency. However, comprehensive validation systems are usually costly and time-consuming.

OBJETIVE

To further evaluate the compliance and reliability of SSI data submitted by using a complementary tool.

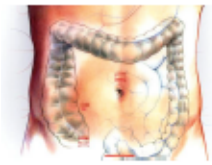
METHODS

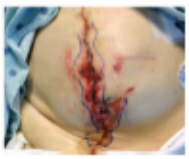
- **Study design:** validation study
- **Setting:** 8 spanish hospitals belonging to the VINCat program.
- **Patients:** 89 Colorectal and 163 Knee prosthesis
- **Definitions:**
  - SSI was defined according to CDC's criteria and divided into superficial and deep incisional SSI and organ-space SSI. Surgical risk factors were defined according to the National Healthcare Safety Network (NHSN) classification.
- **Outcomes:**
  - Main outcome was identifying improvement opportunities and establish a system validation.
  - Secondary outcomes were standard evaluations of structure, protocols and coherence of data .

RESULTS

The VINCat is a surveillance program of HCAI in Catalonia (Spain), based in CDC's NHSN definitions. In addition to standard evaluations of structure, protocols and coherence of data, we validated inclusion of cases and concordance with SSI diagnosis, for elective colorectal surgery and elective knee replacement, in those hospitals with SSI rates below percentile 25. Agreement between external investigators and data of SSI collected by local teams was assessed by reviewing a sample of randomly selected electronic charts.

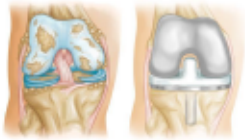
- **Colorectal surgery**

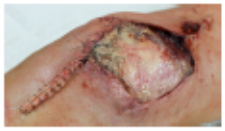




Colorectal surgery (8 hospitals with infection rates below 14.5%): The agreement regarding inclusion (89 cases) was low, 0.32 Kappa index (IC95% 0.05-0.60) and regarding SSI diagnosis (241 cases) was high 0.77 Kappa index (IC95% 0.64-0.89). For SSIs in colo-rectal surgery, the agreement on the inclusion of cases between VINCat external reviewers and ICT was moderate due to differences in the interpretations of inclusion/exclusion criteria, although concordance of SSI data was very high.

- **Knee prosthesis**





Knee prosthesis (4 with infection rates below 1.6%): The agreement regarding inclusion (163 cases) was moderate, 0.0 Kappa index (IC95%: - 0.6-0.6) and SSI diagnosis (121 cases) was good, 0.74 Kappa index (IC95% -1.01-2.63). For knee replacement, agreement on the inclusion cases and SSI data between VINCat external reviewers and ICT was very high. These results show a high quality of process surveillance and data results and provide the basis for identifying improvement opportunities and establish a system validation.

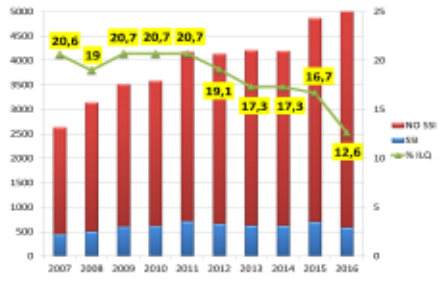


Figure 1. SSI colo-rectal

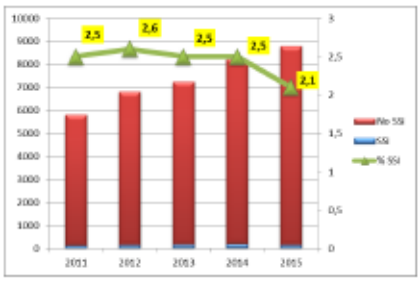


Figure 1. SSI Knee

CONCLUSIONS

On-site visits focused on hospitals suspicious of underreporting allowed determining frequent gaps in the inclusion of patients. Misclassification of type of SSI (superficial, deep or organ/space) was observed in knee procedures, particularly for deep incisional versus organ/space. Surveillance focusing hospitals with rates below percentile 25 appears to be an effective and sustainable tool

Annex V

Predictive factors for mortality among non-ICU patients with catheter-related bacteraemia. Impact on: host, pathogen and therapy

P.Saliba[1], A. Hornero[1], M. Pujol[1] on behalf of REIPI
[1]Infection Control Team, [2]Microbiology Service, Hospital Universitari de Bellvitge, Hospitalet de Llobregat (BARCELONA), Spain

INTRODUCTION

Among all hospital acquired infections ,Catheter related bacteraemia or CRB are considered the most common infections and a major threat to the patients' safety. Episodes of CRB are encountered equally, if not higher, in non-Intensive care units "ICUs" as inside the ICUs. While we have a lot of information regarding the impact of CRB among the ICU patients, the impact of these infections on the non-ICU patients is still in question.

OBJECTIVE

To determine predictors of mortality among non-ICU patients with CRB.

MATERIAL AND METHOD

Patients and Setting

➤**Setting:** The University Hospital of Bellvitge is a 700-bed tertiary centre located in Barcelona area, Spain. An average of 28.000 patients (about 340.000 patient-days) are admitted each year in 31 specialties units, 9 medical and 22 surgical for a mean length of hospital stay of 8.5 days.

➤**Period of Study:** From January 2004 to December 2014, a prospective continuous surveillance of CRB including all adult patients admitted to non-ICU wards for more than 48h, was carried out. Monitoring of CRB was performed by daily meeting of members of the Infection Control Team and members of the microbiology department. Patients with positive blood cultures were visited and those cases that fulfilled criteria for CRB were selected. Patients were followed up until discharge. (not more?)

➤**Catheter-Related Bacteraemia:** A CRB was diagnosed in a suggestive clinical condition, when growth of concordant bacterial species in a semi-quantitative tip culture and percutaneous draw blood culture was observed, without another apparent source of bacteraemia. In the absence of catheter tip culture the diagnosis of CRB required one or more of the following conditions: i) phlebitis, ii) clear resolution of clinical symptoms after catheter withdrawal and a careful exclusion of an alternative explanation for bacteraemia. For common skin microorganisms such as Coagulase Negative Staphylococci (CoNS), at least two consecutive blood cultures were required.

➤**Mortality:** Mortality was defined as in-hospital death from any cause occurring in the 30 days after the onset of CRB.

Statistical Analysis

Among patients with CRB, a logistic regression model was performed to identify risk factors for mortality.

RESULTS

From 2004 to 2014, 546 episodes of CRB were detected in 537 non-ICU patients; 285 in medical wards and 305 in surgical wards.
Mean age was 64y (SD 14y) and 37% were females. Mortality was 16.1%.

Type of catheter

Among all episodes of CRB, 332 (56%) were caused by central venous catheter (19% subclavian, 17% jugular, 12% femoral, 8% peripheral inserted central catheter) and 258 (44%) by peripheral venous catheter.

Microbiology

Gram positive cocci caused 72% of episodes, Gram negative bacilli 28% and fungi 1%. Among them, *S.aureus* was identified in 235 episodes (40%), coagulase negative in 174 (29%), enterococci in 23 (4%), *Pseudomonas aeruginosa* in 33 (6%) and Candida spp in 7 episodes (1%).

Risk factors for mortality. Univariate analysis (Table)

	Alive n=495	Death n= 95	p
Age: <65/ >65 y	89%/80%	11%/20%	**0.003**
Sex (M/F)	83%/85%	17%/15%	NS
Medical W/Surgical W	80%/88%	20%/12%	**0.007**
CVC (n=332)	280 (84%)	52 (16%)	NS
PVC (n=258)	215 (83%)	43 (17%)	NS
Subclavian (n=115)	99 (86%)	16 (14%)	NS
Jugular (n=100)	84 (84%)	16 (16%)	NS
Femoral (n=71)	59 (83%)	12 (17%)	NS
PICC (n=46)	38 (83%)	8 (17%)	NS
Gram Positive Cocci (n=428)	350 (82%)	78 (17%)	**0.024**
Gram Negative Bacilli (n=166)	145 (87%)	21 (13%)	0.172
Candida spp (n=7)	4 (57%)	3 (43%)	0.08
S.aureus (n=235)	174 (74%)	61 (26%)	**<0.001**
MRSA (n=42)	26 (62%)	16 (38)	**<0.001**
CNS (N=174)	161 (92.5%)	13 (7.5%)	**<0.001**
Enterococci spp (n=23)	17 (74%)	6 (26%)	NS
P.aeruginosa (n=33)	27 (82%)	6 (18%)	NS

Risk factors for mortality

Independent risk factors associated to mortality in multivariate analysis were: age older than 65y (OR:2.0;95%CI:1.2-3.2), hospitalization in medical wards (OR:1.6; 95CI:1.0-2.6) and *S.aureus* (OR:3.1; 95%CI:1.9-5.0), while type of catheter and place of insertion were not.

CONCLUSIONS

Among non-critically-ill patients with CRB, those older than 65y, hospitalized in medical wards and with *S.aureus* aetiology had a greater risk of mortality.

Generalitat de Catalunya Departament de Salut
Institut Català de la Salut Gerència Territorial Metropolitana Sud
Bellvitge Hospital Universitari
IDIBELL Institut d'Investigació Biomèdica de Bellvitge
Universitat de Barcelona

Annex VI

CERTIFICADO DE PARTICIPACIÓN

La Presidenta del Comité Organizador del **XXII** Congreso **SEIMC 2018**, en nombre de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica

CERTIFICA QUE:

E. Limón Cáceres, M. Serrano, P. Gallego Berciano, P. Sanchez Ferrin, I. Bullich, P. Saliba, F. Barcenilla, M. Pujol Rojo, F. Gudiol Munté, -. Vincat Group

han realizado la presentación POSTER de la comunicación con título:

"Estudio de prevalencia de las infecciones relacionadas con la asistencia sanitaria en centros sociosanitarios de Cataluña siguiendo al metodología del ECDC"

en el XXII Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, celebrado en Bilbao, del 24 al 26 de mayo de 2018.

Y para que conste se expide el presente certificado en Bilbao a 26 de mayo de 2018.

DOCUMENTO FIRMADO DIGITALMENTE

Dra. Josefa Muñoz Sánchez
Presidenta del Comité Organizador

0370

Annex VII

PROVINCIA AUTONOMA DI TRENTO

FONDAZIONE BRUNO KESSLER

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Certificate of attendance

We hereby confirm that

Patrick Saliba

attended:

Workshop Anti-Superbugs

Trento, 31 January 2018

Fondazione Bruno Kessler
Trento

Dr. Emanuele Torri
Responsabile Scientifico del Progetto

Annex VIII

CER Comitè d'Ètica de Recerca | Universitat Internacional de Catalunya

APROVACIÓ PROJECTE PEL CER/ APROBACIÓN PROYECTO POR EL CER

Codi de l'estudi / *Código del estudio*: CSAL-2018-03
Versió del protocol / *Versión del protocolo*: 1.0
Data de la versió / *Fecha de la versión*: 20/04/2018
Títol / *Título*: The epidemiology of catheter related bloodstream infectos in Bellvitge University Hospital: Prevention and mortality.

Sant Cugat del Vallès, 7 de maig de 2018

Investigador: Patrick Saliba
Director de Tesis: Dr Miquel Rojo Pujol
Co-director:Dr Jose Martinez Sanchez

Títol de l'estudi / *Título del estudio*: The epidemiology of catheter related bloodstream infectos in Bellvitge University Hospital: Prevention and mortality

Benvolgut/da,

Valorat el projecte presentat, el CER de la Universitat Internacional de Catalunya, considera que, el contingut de la investigació, no implica cap inconvenient relacionat amb la dignitat humana, tracte ètic per als animals ni atempta contra el medi ambient, ni té implicacions econòmiques ni conflicte d'interessos, **però no s'han valorat els aspectes metodològics del projecte de recerca degut a que tal anàlisis correspon a d'altres instàncies.**

Per aquests motius, el Comitè d'Ètica de Recerca, RESOLT FAVORABLEMENT, emetre aquest CERTIFICAT D'APROVACIÓ, per que pugui ser presentat a les instàncies que així ho requereixin.

Em permeto recordar-li que, si en el procés d'execució es produís algun canvi significatiu en els seus plantejaments, hauria de ser sotmès novament a la revisió i aprovació del CER.

Atentament,

Apreciada,

Valorado el proyecto presentado, el CER de la Universidad Internacional de Catalunya, considera que, el contenido de la investigación, no implica ningún inconveniente relacionado con la dignidad humana, trato ético para los animales, ni atenta contra el medio ambiente, ni tiene implicaciones económicas ni conflicto de intereses, ***pero no se han valorado aspectos metodológicos del proyecto de investigación debido a que tal análisis corresponde a otras instancias.***

Por estos motivos, el Comitè d'Ètica de Recerca, RESUELVE FAVORABLEMENTE, emitir este CERTIFICADO DE APROBACIÓN, para que pueda ser presentado a las instancias que así lo requieran.

Me permito recordarle que si el proceso de ejecución se produjera algún cambio significativo en sus planteamientos, debería ser sometido nuevamente a la revisión y aprobación del CER.

Atentamente,

Dr. Josep Argemí
President CER-UIC