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Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study

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Abstract *Objective:* To assess the risk factors associated with CR-BSI development in critically ill patients with non-tunneled, non-cuffed central venous catheters (CVC) and the prognosis of the episodes of CR-BSI. Design and setting; prospective, observational, multicenter study in nine Spanish Hospitals. *Patients:* All subjects admitted to the participating ICUs from October 2004 to June 2005 with a CVC. *Interventions:* None. *Measurement and results:* Overall, 1,366 patients were enrolled and 2,101 catheters were analyzed. Sixty-six episodes of CR-BSI were diagnosed. The incidence of CR-BSI was significantly higher in CVC compared with peripherically inserted central venous catheters (PICVC) without significant differences among the three locations of CVC. In the multivariate analysis, duration of catheterization and change over a guidewire were the independent variables associated with the development of CR-BSI whereas the use of a PICVC was a protective factor. Excluding PICVC, 1,598 conventional CVC were analyzed. In this subset, duration of catheterization, tracheostomy and change over a guidewire were independent risk factors for CR-BSI. A multivariate analysis of predictors for mortality among 66 patients with CRSI showed that early removal of the catheter was a protective factor and APACHE II score at the admission was a strong determinant of in-hospital mortality. *Conclusions:* Peripherically inserted central venous catheters is associated with a lower incidence of CR-BSI in critically ill patients. Exchange over a guidewire of CVC and duration of catheterization are strong contributors to CR-BSI. Our results reinforce the importance of early catheter removal in critically ill patients with CR-BSI.

Keywords Bacteremia · Catheter · Peripherically inserted central venous catheters · Catheter-related bloodstream infection · Risk factor · Prognosis

Introduction

Although central vascular catheters (CVCs) are often indispensable for the management of critically ill patients, their use is associated with diverse and potentially lethal complications. The most serious infectious problem is catheter-related bloodstream infection (CR-BSI), which prolongs hospital stay, increases costs of hospitalization and may lead to death in selected patients [1]. The pathogenesis of CR-BSI is complex. Outer surface of CVC may become colonized with organisms from the skin. The catheter lumen is usually colonized later from bacteria entering the catheter hub [2]. On the basis of current knowledge on pathogenesis, prevention strategies have become a major issue to reduce the incidence of CR-BSI.

Identification of risk factors associated with CR-BSI is essential to implement intervention programs in order to reduce the incidence of this complication. Although there are many studies about CR-BSI risk factors, very few have analyzed them exhaustively in critically ill patients. Most of these studies have been conducted at single institutions, and only a limited number of risk factors have been examined [3–6]. In fact, large prospective studies addressing all potential risk factors have been recently demanded to enhance our strategies for CR-BSI prevention [7]. In addition, information about prognostic factors of CR-BSI in critical care patients is scarce [8]. This issue can be of great clinical value for the management of patients with catheter-associated bacteremia.

The objectives of the present study were to assess the risk factors associated with CR-BSI development in a large cohort of critically ill patients with non-tunneled, non-cuffed CVC and the prognosis of these episodes of CR-BSI. This research has been presented, in part, in a recent international meeting [9].

Methods

This is a prospective multicenter observational study carried out in the intensive care units of nine Spanish hospitals. All these hospitals except one were large institutions with teaching accreditation. The study was conducted from October 2004 to June 2005. A meeting was held in Seville in order to discuss the protocol and to homogenize the insertion and care of the CVC based on current guidelines [10] (Table 1). Exchange over a guidewire of a CVC was considered acceptable only to replace a malfunctioning catheter without infection suspiction. Although tip culture of removed catheter is the correct practice, this recommendation was not specifically included in the protocol. Only percutaneously inserted CVCs were objective of the present study including central venous catheter and peripherally inserted CVC.

Table 1 Standardized protocol for catheter insertion and care in the nine participating Units

- Hand-hygiene either with conventional antiseptic-containing soap and water or with waterless alcohol-based solutions.
- Maximal sterile barrier precautions during catheter placement are always required. These safety measures include aseptic technique with the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet, for the insertion of CVCs (including PICVC).
- At the time of catheter placement, skin was cleaned with povidone–iodine or chlorhexidine depending on the product available in each institution.
- All catheters inserted in clinically urgent situations without maximal sterile barrier precautions should be replaced as soon as possible.
- Antibiotic impregnated catheters or chlorhexidine-impregnate sponges were not allowed during the present study in any institution.
- Catheter dressing are replaced when it becomes damp or soiled or when inspection of the site is necessary.
- Gauze dressing must be changed every 48 h and semi-transparent dressings every 7 days.
- Clean or sterile gloves must be worn to perform dressing change.
- Guidewire-assisted catheter exchange to replace a malfunctioning catheter is acceptable if there is no evidence of infection. However, if infection is suspected, the existing catheter should be removed and a new catheter should be inserted at a different site.
- Routinely replacement of CVC to prevent CR-BSI is not permitted.
- Replace administration sets every 72 h.
- Replace administration sets used to administer blood products, total parenteral nutrition or propofol within 24 h of initiating the infusion.
- In-line filters are not allowed.

Catheters inserted in emergency situations were excluded from the present study.

Our objective was to determine the risk factors associated with CR-BSI development in critically ill patients. For this analysis, baseline characteristics, previous comorbidities, factors related to catheter insertion, catheter characteristics, and maintenance and use of the catheter were recorded. We also assessed the prognosis of the episodes of CR-BSI. For this purpose, baseline characteristics, previous comorbidities, severity of illness at the admission and the day of bacteremia, management of CR-BRSI, and outcome were noted.

Data collection

After inclusion in this study, catheters were tracked with a form containing all variables and data that were stored on a database available at (http://www.reipi.org/private).

Variables

(a) Baseline characteristics: age, gender, type of patients (surgical, medical, trauma, burn, or coronary patient), underlying illnesses following previous definitions

[11]. Severity of the illness at admission was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score considering the worst data point of the first 24 h in the ICU [12].

(b) Factors related to the catheter insertion: anatomic site of insertion, new puncture or change over a guidewire, catheter insertion in the ICU or out of the ICU (emergency room, operating room, or general ward), experience of the operator (resident or staff), antiseptic for skin cleansing (chlorhexidine or povidone-iodine), difficulty of insertion [13], and time of placement (day or night). Moreover, the presence of tracheostomy, mechanical ventilation, and antibiotic administration on the day of insertion was also registered.

(c) Factors related to the catheter characteristics: number of lumens, material (polyurethane or polyvinyl)

(d) Factors related to the catheter maintenance and use: presence of three-way stopcock, use to measure central venous pressure, administration of total parenteral nutrition (TPN), propofol, hemoderivates, or antimicrobials through the catheter.

Other variables were noted to assess the prognosis of an episode of CR-BSI: severity of organ dysfunction evaluated by Sequential Organ Failure Assessment (SOFA) scale on the day of CR-BSI diagnosis [14], delay of catheter withdrawal, and adequacy of empirical antimicrobial therapy. Therapy was considered inadequate when no effective drug against the isolated pathogen(s) was included in the empirical antibiotic treatment within the first 24 h after the diagnosis. Early removal was considered when the infected catheter was removed in the first 24 h after the positive blood culture was drawn and late removal when the catheter withdrawal was performed after 24 h.

All patients were followed up until death or hospital discharge.

Diagnosis of CR-BSI

The decision to remove the catheter was made by the patient's physician. CR-BSI was diagnosed following current criteria [15]. Briefly, CR-BSI required positive blood culture obtained from a peripheral vein and positive semiquantitative tip culture (>15 CFU) or positive quantitative tip culture (>10^3 CFU). Simultaneous quantitative cultures of blood samples obtained through suspected catheter and peripheral vein with a ratio ≥5:1 or a differential time to positivity ≥120 min in blood cultures drawn simultaneously through the catheter and a peripheral vein were also considered diagnostic of CR-BSI.

Statistical analysis

Predictive risk factors were evaluated for CR-BSI in CVC courses. CR-BSI cases were compared with CVC without CR-BSI. The Fisher exact test was used to determine significant differences among categorical variables. We expressed continuous variables as mean (±SD) or median and interquartile range (IQR), if their distributions were skewed. We compared groups using the unpaired Student's t test for normally distributed variables after correction for equality of variance (Levene's test) or the Mann–Whitney U test for non-normally distributed continuous variables when indicated. Comparisons of the CR-BSI incidence per 1,000 catheter days among the different venous accesses were carried out by Poisson distribution and test-based methods [16].

Variables with P value below 0.1 in the univariate analysis were entered into the logistic regression model to identify risk factors independently associated with CR-BSI. The odds-ratio (OR) and their corresponding 95% confidence intervals (95% CI) were also calculated.

Moreover, risk factors for in-hospital mortality were assessed by univariate analysis in those patients with CR-BSI. Variables with P value below 0.1 in this univariate analysis were entered into the logistic regression model to determine the factors independently associated with in-hospital mortality.

The software packages used for statistical analysis were SPSS for Windows version 14.0 (SPSS Inc, Chicago, Ill) and EPIDAT version 3.1.

Results

During the study period, 1,373 patients were enrolled in the present study. Only 1,366 were analyzed, of whom 64.7% were males. The mean age was 61.3 (16.3) years; APACHE II score was 13.7 (7.4). ICU mortality was 18.8% (257 patients) and crude in-hospital mortality was 24.2% (331 patients).

Altogether, 2,187 CVC were included although 86 catheters were excluded from the analysis due to incomplete information. Therefore, 2,101 catheters were analyzed and observed during 20,981 patient-days: 626 were placed in jugular vein, 585 in subclavian vein, 387 in femoral vein, and 503 were peripherally inserted central venous catheters (PICVC).

During the study period, 66 episodes of CR-BSI were diagnosed (3.02% of the inserted catheters). The microorganisms involved were; Coagulase-negative *staphylococci* (35), *Acinetobacter baumannii* (11), *Staphylococcus aureus* (5), *Candida* spp. (4), *Pseudomonas aeruginosa* (4), *Enterococcus faecalis* (3), *Klebsiella pneumoniae* (3), *Enterobacter* spp. (2), others (4). Five bacteremias were polymicrobial. Rates of CR-BSI did not differ among the nine participating ICUs. The overall incidence of CR-BSI

was 3.15 per 1,000 catheter days. The incidence in PICVC was 1.07 per 1,000 catheter days [95% confidence interval (CI), 0.13–2.01] and 3.73 episodes per 1,000 catheter days (95% CI, 2.8–4.67) in conventional CVC ($P = 0.007$).

Risk factors for CR-BSI development

Table 2 shows the analysis of risk factors for CR-BSI. The incidence of CR-BSI was significantly higher in CVC compared with PICVC (3.8 vs. 1%; $P = 0.001$) without significant differences among the three locations of CVC. The ratio of incidence rates in conventional CVC versus PICVC was 3.480 (95% CI 1.398–8.661; $P = 0.006$).

Factors associated with the development of CR-BSI were: change over a guidewire, insertion of the catheter by a staff member, tracheotomy, mechanical ventilation, and the use of the catheter to administer TPN. Duration of catheterization was significantly longer in conventional CVC than in PICVC [8 days (5–13) vs. 7 days (5–11); $P = 0.001$].

However, using multiple logistic regression analysis, duration of catheterization and change over a guidewire were the independent variables associated with the development of CR-BSI whereas the use of a PICVC was a protective factor (Table 2).

Risk factors for CR-BSI development (excluding PICVC)

Excluding PICVC, 1,598 conventional CVC were analyzed. Patient characteristics and underlying diseases did not significantly differ between catheter with CR-BSI and those without associated bacteremia. The incidence densities of CR-BSI in the subclavian, jugular, and femoral accesses are shown in Table 2. The ratios of incidence rate were not statistically different among the three sites: jugular versus subclavian access 0.823 (95% CI 0.446–1.517; $P = 0.638$); jugular versus femoral 0.737 (95% CI 0.380–1.430; $P = 0.460$) and subclavian versus femoral 0.895 (95% CI 0.490–1.633; $P = 0.837$).

Table 3 shows risk factors of CR-BSI in relation to catheter characteristics, insertion, and subsequent catheter use. Thirteen patients with tracheostomy developed CR-BSI: seven subclavian catheters, five femoral catheters, and one jugular catheter. In comparison with those patients without tracheostomy, length of stay before catheterization was significantly longer in those with tracheostomy ($P < 0.0001$).

Multiple logistic regression analysis identified duration of catheterization, tracheostomy, and change over a guidewire as independent risk factors for CR-BSI (Table 3).

Clinical presentation and outcome of CR-BSI

Sixty-six patients developed CR-BSI in the ICU. Median time from insertion of the catheter to the development of bacteremia was 10 days. CR-BSI presented as septic shock in 21 patients and in four subjects clinical response did not fulfill sepsis criteria. Eighteen patients died in the ICU (27.3%). In-hospital mortality was 33.3%.

Univariate analysis of factors associated with mortality in patients with CR-BSI is shown in Table 4. APACHE II score was similar ($P = 0.8$) in patients with early (13.4 ± 6.5) or late removal (13.1 ± 4.7). SOFA score on the day of diagnosis tended to be higher ($P = 0.09$) in patients with early removal (6.2 ± 4.6) than in patients in whom the catheter was removed after 24 h (4 ± 2.9). The median delay of catheter removal in those patients in whom the catheter was not removed within the first 24 h was 3 days (IQR 2–4 days).

Analyzing patients with coagulase-negative *Staphylococci* bacteremia, mortality rate was similar ($P = 0.999$) in patients with early (6/21; 28.6%) or late removal (3/9; 33.3%). In patients with non-coagulase-negative *Staphylococci* CR-BSI, mortality was significantly higher ($P = 0.046$) in patients with late catheter removal (6/9; 66.6%) than in those subjects in whom the responsible device was withdrawn within the first 24 h (7/27; 25.9%). On the other hand, in patients with septic shock, mortality was significantly higher ($P = 0.032$) in patients with late catheter removal (6/6; 100%) than in those patients in whom the catheter was withdrawn within the first 24 h (7/15; 46.7%). However, mortality was not statistically different in patients without septic shock (18.2 vs. 25%; $P = 0.450$).

In the multivariate analysis, early removal of the catheter was a protective factor and APACHE II score was an independent determinant of in-hospital mortality (Table 4). Excluding from the analysis those four patients without criteria of sepsis, mortality was significantly lower in patients with early removal compared to those patients in whom the catheter was removed after 24 h (26.1 vs. 56.3%; $P = 0.036$) and the multivariate analysis did not change, confirming that APACHE II score and early removal of the catheter were the factors independently associated with in-hospital mortality.

Discussion

According to the findings of this large multicenter study, PICVC is a safe venous access in critically ill patients because its use is associated with a lower incidence of bacteremia. Exchange over a guidewire of central venous catheters is a strong contributor to CR-BSI, so it cannot be advocated for routine use in the ICU. In addition, our

Table 2 Risk factors for CR-BSI development

Variable	Univariate analysis			Multivariate analysis	
	CR-BSI ($n = 66$) [*N* (%)]	No CR-BSI ($n = 2035$) [N (%)]	*P* value	*P* value	OR (95% CI)
Age, mean (SD)	56.9 (16.2)	59.2 (16.4)	0.244	–	
APACHE II, mean (SD)	13.2 (6)	14.5 (7.1)	0.458	–	
Gender (male)	50 (75.8)	1,343 (66)	0.112	–	
Type of patients			0.171	–	
Surgical	31 (46.9)	997 (49)			
Medical	20 (30.4)	585 (28.7)			
Others	15 (22.7)	453 (22.3)			
Comorbidities					
Diabetes mellitus	13 (19.7)	402 (19.8)	0.999	–	
COPD	5 (7.6)	315 (15.5)	0.090	0.120	
Liver cirrhosis	5 (7.6)	142 (7)	0.805	–	
ESRD	1 (1.5)	59 (2.9)	0.999	–	
CHF	9 (13.6)	264 (13)	0.852	–	
Immunosuppression	2 (3)	154 (7.6)	0.231	–	
Cancer	7 (10.6)	360 (17.7)	0.186	–	
Place of catheter insertion			0.003	–	
Jugular vein	17 (25.8)[a]	609 (29.9)			
Subclavian vein	26 (39.4)[b]	559 (27.5)			
Femoral vein	18 (27.3)[c]	369 (18.1)			
PICVC	5 (7.6)[d]	498 (24.5)			
Type of catheter			0.001		
PICVC	5 (7.6)[d]	498 (24.5)		0.008	0.29 (0.11–0.72)
Conventional CVC	61 (92.4)[e]	1,537 (75.5)			
Catheter insertion					
Change over a guidewire	11 (16.7)	65 (3.2)	<0.0001	0.0001	4.59 (2.28–9.3)
Insertion out of the ICU	17 (25.7)	624 (30.6)	0.300	–	
Time of placement (night)	15 (22.7)	382 (16.1)	0. 425	–	
Very difficult insertion	4 (6)	134 (6.6)	0.999	–	
Insertion by a staff member	28 (46.7)	572 (29.6)	0.010	0.129	
Tracheotomy	13 (19.7)	160 (9.7)	0.002	0.081	
Mechanical ventilation	48 (72.7)	1,201 (59)	0.030	0.364	
Antibiotic administration	49 (81.7)	1,343 (71.5)	0.115	–	
Administration of a glycopeptide	10 (15.2)	235 (11.5)	0.334	–	
Number of lumens			0.110	–	
Single-lumen	7 (10.6)[f]	405 (19.9)			
Double-lumen	19 (28.8)[g]	618 (30.4)			
Triple-lumen	40 (57.6)[h]	1,012 (49.7)			
Material polyurethane	65 (98.5)	1,991 (97)	0.999	–	
Antiseptic			0.077	0.064	
Chlorhexidine	3 (4.5)	239 (11.7)			
Povidone–iodine	63 (95.5)	1,796 (88.3)			
Use of three-way stopcock	65 (98.5)	1,953 (96)	0.517	–	
Use to measure CVP	29 (43.9)	1,131 (55.6)	0.078	0.066	
Concomitant infection	32 (48.5)	952 (46.7)	0.803	–	
Duration of catheterization (days)	11 (8–16)	8 (5–12)	$P < 0.0001$	0.003	1.028 (1.009–1.048)
Catheter use for administration of					
TPN	19 (28.8)	349 (17.1)	0.021	0.155	
Propofol	22 (33.3)	464 (22.8)	0.053	0.350	
Hemoderivates	13 (19.7)	313 (15.4)	0.386	–	
Antimicrobials	54 (81.8)	1,493 (73.4)	0.155	–	

CR-BS catheter-related bloodstream infection, *OR* odds-ratio, *SD* standard deviation, *APACHE* acute physiology and chronic health evaluation, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease, *CHF* chronic heart failure, *PICVC* peripherically inserted central venous catheter, *CVC* central venous catheter, *ICU* intensive care unit, *CVP* central venous pressure, *TPN* total parenteral nutrition

[a] 3.16 per 1,000 catheter days (95% CI, 1.66–4.67)

[b] 3.84 per 1,000 catheter days (95% CI, 2.37–5.32)

[c] 4.29 per 1,000 catheter days (95% CI, 2.31–6.28)

[d] 1.07 per 1,000 catheter days (95% CI 0.13–2.01)

[e] 3.73 episodes per 1,000 catheter days (95% CI, 2.8–4.67)

[f] 1.97 episodes per 1,000 catheter days (95% CI, 0.51–3.45)

[g] 2.86 episodes per 1,000 catheter days (95% CI, 1.58–4.15)

[h] 3.70 episodes per 1,000 catheter days (95% CI, 2.56–4.85)

Table 3 Risk factors associated with CR-BSI in conventional central venous catheters

Variable	Univariate analysis			Multivariate analysis	
	CR-BSI ($n = 61$) [N (%)]	No CR-BSI ($n = 1{,}537$) [N (%)]	P value	P value	OR (95% CI)
Site of insertion			0.18	–	
Jugular vein	17 (27.9)	609 (39.6)			
Subclavian vein	26 (42.6)	559 (36.4)			
Femoral vein	18 (29.5)	369 (24)			
Catheter insertion					
Change over a guidewire	11 (18)	65 (4.2)	<0.0001	<0.0001	4.15 (2.02–8.5)
Insertion out of the ICU	7 (22.3)	333 (11.4)	0.056	0.337	
Time of placement (night)	15 (22.7)	382 (18.7)	0.999		
Very difficult insertion	4 (6)	134 (6.5)	0.999	–	
Insertion by staff member	28 (45.9)	561 (36.5)	0.220	–	
Tracheostomy	13 (21.3)	121 (7.9)	0.001	0.016	2.3 (1.17–4.54)
Mechanical ventilation	46 (75.4)	977 (63.6)	0.076	0.336	
Antibiotic administration	45 (80.4)	998 (70.2)	0.134	–	
Administration of a glycopeptide	9 (14.8)	185 (12)	0.540	–	
Number of lumens			0.34	–	
Single-lumen	2 (3.3)[a]	18 (1.2)			
Double-lumen	19 (31.1)	507 (33)			
Triple-lumen	40 (65.6)	1,012 (65.8)			
Material polyurethane	58 (95.1)	1,501 (97.7)	0.999	–	
Antiseptic			0.199	–	
Chlorhexidine	3 (4.9)	161 (10.5)			
Povidone–iodine	58 (95.1)	1,376 (89.5)			
Use of three-way stopcock	61 (100)	1,475 (96)	0.169	–	
Use to measure CVP	28 (45.9)	910 (55.6)	0.046	0.105	
Concomitant infection	28 (45.9)	696 (45.3)	0.999	–	
Duration of catheterization (days)	12 (8–17)	8 (5–13)	<0.0001	0.017	1.029 (1.005–1.053)
Catheter use for administration of					
TPN	18 (29.5)	304 (19.8)	0.073	0.434	
Propofol	20 (32.8)	386 (25.1)	0.179	–	
Hemoderivates	13 (21.3)	285 (18.5)	0.615	–	
Antimicrobials	50 (82)	1,135 (73.8)	0.180	–	

CR-BS catheter-related bloodstream infection, *OR* odds-ratio, *ICU* intensive care unit, *CVP* central venous pressure, *TPN* total parenteral nutrition

[a] 1.14 episodes per 1,000 catheter days (95% CI, −0.44–2.73). Other incidence densities are depicted in Table 2

Table 4 Univariate and multivariate analyses of factors associated with in-hospital mortality in patients with CR-BSI

Variable	Univariate analysis			Multivariate analysis	
	Survivors ($n = 44$) [N (%)]	Non-survivors ($n = 22$)	P value	P value	OR (95% CI)
Age[a]	53.1 (17.6)	65.1 (13.3)	0.008	0.074	
APACHE II[a]	11.7 (6)	16.2 (4.9)	0.006	0.015	1.17 (1.03–1.33)
Gender (male)	34 (77.3)	16 (72.2)	0.764	–	
Diabetes mellitus	6 (13.6)	7 (31.8)	0.105	–	
COPD	3 (6.8)	2 (9.1)	0.999	–	
Cirrhosis	5 (11.4)	1 (4.5)	0.655	–	
ESRD	1 (2.3)	0 (0)	0.999	–	
CHF	7 (15.9)	2 (9.1)	0.706	–	
Immunosuppression	0 (0)	2 (9.1)	0.108	–	
Cancer	6 (10.6)	1 (4.5)	0.409	–	
SOFA score (day of CR-BSI)[a]	5.94 (5.1)	5.4 (3.96)	0.662	–	
Adequate empirical therapy	22 (50)	10 (45.5)	0.797	–	
Early removal (<24 h)	35 (79.5)	13 (59.1)	0.089	0.030	0.22 (0.1–0.86)

[a] Mean (SD) COPD denotes chronic obstructive pulmonary disease

ESRD end-stage renal disease, *CHF* chronic heart failure, *CR-BS* catheter-related bloodstream infection

results highlight the importance of early catheter removal as a measure to improve the outcome of critically ill patients with CR-BSI.

Although several studies have addressed the question of which factors are associated with CR-BSI in different clinical settings, there is little information in critically ill patients. Maximal barrier precautions during catheter insertion are universally accepted as efficacious measures to reduce the risk for CR-BSI [10]. These measures were standardized in the present study.

The use of PICVCs has gained acceptance as a method for venous access in critically ill patients. Whether PICVCs are associated with a lower risk of CR-BSI than conventional CVCs is still a matter of debate. Of note, our incidence rate of CR-BSI of PICVCs is 1.07 episodes per 1,000 catheter days which is in the lower range of the incidence reported by Maki et al. [17] by grouping 625 PICVC in hospitalized patients. Two recent studies, in critically ill patients, concluded that the rate of CR-BSI was similar with these two types of venous accesses [18, 19]. Our findings do not support these observations and in the critical care settings, the use of PICVCs is a suitable alternative, especially in less severely ill patients, because it is associated with a lower incidence of CR-BSI.

The use of propofol and TPN was associated with a higher incidence of CR-BSI in the univariate analysis. Propofol is a sedative agent that may cause alterations of bacterial clearance attributable to the lipid vehicle [20]. Antibiotic administration via the catheter did not decrease the risk of bacteremia as reported in a trial that evaluated complications of femoral and subclavian venous catheterization [21]. Our results do not support the prophylactic use with glycopeptides during catheter insertion [22].

Numerous studies have been conducted to determine the catheter site of insertion associated with higher incidence of CR-BSI. In a randomized controlled trial, femoral venous catheterization was associated with a greater risk of overall infectious complications compared to the subclavian access although the rate of CR-BSI was similar in both groups [21]. Likewise, observational studies also concluded that the risk of CR-BSI was higher in the femoral access than in the jugular or subclavian vein [6, 18]. In contrast, other studies [23–26], in agreement with our results, concluded that the incidence of CR-BSI is not different at the three sites. It may indicate that the use of strict sterile insertion precautions, the standardized continuous catheter care, and the duration of catheterization are more determinant for CR-BSI occurrence that the anatomic site.

Diverse studies evaluating chlorhexidine-containing cutaneous antiseptic regimens in comparison with povidone–iodine have shown lower rates of CR-BSI associated with the chlorhexidine preparations [27, 28]. Overall, we found a lower incidence of CR-BSI using chlorhexidine and although this factor was not included in the final model, there was a statistically almost significant trend towards decreased incidence of CR-BSI with this antiseptic in the multivariate analysis. This may be explained by the low number of cases in which this antiseptic was used.

In agreement with previous studies [29–31], we identified the duration of catheterization as an independent determinant for CR-BSI. More importantly, as compared with new-site replacement, guidewire exchange was associated with a greater risk of CR-BSI. In a systematic review 12 randomized trials, guidewire exchange of CVC was associated with a greater risk of catheter-related infection including CR-BSI than a new venipuncture [32]. This risk factor has also been reported in pediatric populations [33, 34], although other studies do not support association [35, 36]. Therefore, a guidewire exchange should be avoided even when catheter infection is not clinically suspected. Nevertheless, guidewire exchange may be performed only in patients in which the diagnosis of CRBSI is as yet uncertain and who are at high risk of mechanical complications during catheter insertion or with very limited venous access.

It is worth noting that tracheotomy was a strong contributor to CR-BSI. Tracheotomy was identified as the only significant variable associated with the colonization of catheters placed in the subclavian vein [37]. Nevertheless, this variable has not been taken into account in the majority of studies evaluating risk factor of CR-BSI in critically ill patients [3–6]. Our finding may be explained by the easy contamination of the catheters in case of subclavian or jugular access in tracheotomized patients. Otherwise, this may reflect the higher density of local skin flora due to the longer hospitalization in tracheotomized patients.

Two factors have been identified in the present study as having prognostic importance in patients with CR-BSI. Optimal CRBSI management consists in catheter removal and appropriate empirical antimicrobial therapy. The election of the antibiotics must be done on the basis of clinical suspicion, underlying diseases, and local ecology. In our analysis, early catheter removal has important prognostic consequences because it is a protective factor of mortality. In a recent controlled trial, hemodynamically stable patients without proven bacteremia were randomized to standard care or a watchful waiting strategy following a clinical protocol. ICU mortality was similar with both approaches and this trial was not designed to detect differences in mortality [38].

Diverse studies have shown that CVC removal is associated with improved outcome in patients with CR-BSI caused by *S aureus*, *Candida* spp. or Gram-negative bacilli although the impact on the outcome of the time elapsed since bacteremia to catheter withdrawal has not been assessed [8]. Obviously, indiscriminate removal of the CVC may result in an unnecessary practice, but clinicians should be aware about the negative impact on the survival of late catheter removal in patients with CR-BSI.

We admit several limitations of the present study. First, proper implementation of hand-hygiene and maximal barrier precautions during the insertion of catheters was not monitored. We cannot guarantee that these essential measures were always observed. Second, these results cannot be generalized to antibiotic-coated catheters, which have been proved to reduce the incidence of CR-BSI [39]. Third, we did not note the exact delay of catheter withdrawal to determine precisely its impact on mortality. Despite these limitations, we present a large multicenter study that shed light on our actual knowledge about risk factors and management of CR-BSI in the critical care setting.

In conclusion, our results should be taken into account when elaborating CR-BSI prevention programs bearing in mind that maximal barrier precautions during catheter insertion and the use of chlorhexidine-containing antiseptics are of proven efficacy. Exchange over a guidewire should be discouraged and specific concern must be assigned to the insertion of a CVC when a tracheotomy is already present. Every day clinicians should evaluate the necessity of all CVCs since duration of catheterization is a strong contributor to CR-BSI. The delay of catheter removal in a critically ill patient with CR-BSI may negatively influence the outcome.

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References

1. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, Decruyenaere J, Vogelaers D, Colardyn F, Vandewoude KH (2005) Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 41:1591–1598
2. Henderson DK (2000) Infections due to percutaneous intravascular devices. In: Mandell GL, Bennet JE, Dolin R (eds) Principles and practice of infectious diseases. Churchill Livingstone, Philadelphia, pp 3005–3020
3. Moro ML, Vigano EF, Cozzi Lepri A (1994) Risk factors for central venous catheter-related infections in surgical and intensive care units. The Central Venous Catheter-Related Infections Study Group. Infect Control Hosp Epidemiol 15:253–264
4. Charalambous C, Swodoba SM, Dick J, Perl T, Lipsett PA (1998) Risk factors and clinical impact of central line infections in the surgical intensive care unit. Arch Surg 133:1241–1246
5. Gowardman JR, Montgomery C, Thirwell S, Shewan J, Idema A, Larsen PD, Havill JH (1998) Central venous catheter-related bloodstream infections: an analysis of incidence and risk factors in a cohort of 400 patients. Intensive Care Med 24:1034–1039
6. Lorente L, Henry C, Martin MM, Jiménez A, Mora ML (2005) Central venous catheter-related infection in a prospective and observational study of 2, 595 catheters. Crit Care 9:R631–635
7. Safdar N, Kluger DM, Maki DG (2002) A review of risk factors for catheter-relayed bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters. Medicine 81:466–479
8. Raad I, Hanna H, Maki DG (2007) Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis 7:645–657
9. Escoresca AM, Aldabo T, Diaz A, Palomar M, Valles J, Graces R, Baquero F, Pujol M, Bouza E, Garnacho J (2007) National multicenter study: risk factors for bacteremia associated with central venous catheter in Intensive Care Unit. Intensive Care Med 33:S102
10. O'Grady NP, Alexander M, Delliger P Gerberding JL, Heard SO, Maki DG, Masur H, McCormick RD, Mermel LA, Pearson ML, Raad II, Randolph A, Weinstein RA; Healthcare Infection Control Practices Advisory Committee (2002) Guidelines for the prevention of intravascular catheter-related infections. Infect Control Hosp Epidemiol 23:759–769
11. Pittet D, Thiévent B, Wenzel RP, Li N, Gurman G, Suter P (1993) Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 19:265–272
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II, a severity of disease classification system. Crit Care Med 13:818–829
13. Langgartner J, Linde HJ, Lehn N, Reng M, Schölmerich J, Glück T (2004) Combined skin disinfection with chlorhexidine/propanol and aqueous povidone-iodine reduces bacterial colonisation of central venous catheters. Intensive Care Med 30:1081–1088
14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707–710
15. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, Craven DE (2001) Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 32:1249–1272
16. Rothman KJ, Greenland S (1998) Modern epidemiology, 2nd edn. Lippincott Williams & Wilkins, Philadelphia
17. Maki DG, Kluger DM, Cmich CJ (2006) The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 81:1159–1171
18. Lorente L, Villegas J, Martín MM, Jimenez A, Mora ML (2004) Catheter-related infection in critically ill patients. Intensive Care Med 30:1681–1684
19. Sadfar N, Maki DG (2005) Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. Chest 128:489–495
20. Kelbel I, Koch T, Weber A, Schiefer HG, van Ackern K, Neuhof H (1999) Alterations of bacterial clearance induced by propofol. Acta Anaesthesiol Scand 43:71–76

21. Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, Rigaud JP, Casciani D, Misset B, Bosquet C, Outin H, Brun-Buisson C, Nitenberg G; French Catheter Study Group in Intensive Care (2001) Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA 286:700–707
22. van de Wetering MD, van Woensel JB, Kremer LC, Caron HN (2005) Prophylactic antibiotics for preventing early Gram-positive central venous catheter infections in oncology patients, a Cochrane systematic review. Cancer Treat Rev 31:186–196
23. Durbec O, Vivand X, Potie F, Vialet R, Albanese J, Martin C (1997) A prospective evaluation of the use of femoral venous catheters in critically ill adults. Crit Care Med 25:1986–1989
24. Goetz AM, Wagner MM, Miller JM, Muder RR (1998) Risk of infection due to central venous catheters: effect of site of placement and catheter type. Infect Control Hosp Epidemiol 19:842–845
25. Deshpande KS, Hatem C, Ulrich HL, Currie BP, Aldrich TK, Bryan-Brown CW, Kvetan V (2005) The incidence of infectious complications of central venous catheters at the subclavian, internal jugular, and femoral sites in an intensive care unit population. Crit Care Med 33:13–20
26. Gowardman JR, Robertson IK, Parkes S, Rickard CM. (2008) Influence of insertion site on central venous catheter colonization and bloodstream infection rates. Intensive Care Med 10.1007/s00134-008-1046-3. Access May 22.
27. Maki DG, Ringer M, Alvarado CJ (1991) Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. Lancet 338:339–343
28. Mimoz O, Pieroni L, Lawrence C, Edouard A, Costa Y, Samii K, Brun-Buisson C (1996) Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. Crit Care Med 24:1818–1823
29. Hammarskjölf F, Wallén G, Malmvald BE (2006) Central venous catheter infections at a county hospital in Sweden: a prospective analysis of colonization, incidence of infection and risk factors. Acta Anaesthesiol Scand 50:451–460
30. Van der Kooi TI, de Boer AS, Manniën J, Wille JC, Beaumont MT, Mooi BW, van den Hof S (2007) Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system. Intensive Care Med 33:271–278
31. Yilmaz G, Koksal J, Aydin K, Caylan R, Sucu N, Aksoy F (2007) Risk factors of catheter-related bloodstream infections in parenteral nutrition catheterization. JPEN 31:284–287
32. Cook D, Randolph A, Kemerman P, Cupido C, King D, Soukup C, Brun-Buisson C (1997) Central venous catheter replacement strategies: a systematic review of the literature. Crit Care Med 25:1417–1424
33. Almuneef MA, Menish ZA, Balkhy HH, HH, Hijazi O, Cunningham G, Francis C (2006) Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. J Hosp Infect 62:207–213
34. Garcia-Teresa MA, Casado-Flores J, Delgado-Dominguez MA, Roqueta-Mas J, Cambra-Lasaosa F, Concha-Torre A, Fernández-Pérez C; Spanish Central Venous Catheter Pediatric Study Group (2007) Infectious complications of percutaneous central venous catheterization in pediatric patients: a Spanish multicenter study. Intensive Care Med 33:466–476
35. Hagly MT, Martin B, Gast P, Traeger SM (1992) Infectious and mechanical complications of central venous catheters placed by percutaneous venipuncture and over guidewires. Crit Care Med 20:1426–1430
36. O'Mara MS, Reed NL, Palmieri TL, Greenhalgh DG (2007) Central venous catheter infections in burn patients with scheduled catheter exchange and replacement. J Surg Res 142:341–350
37. Michel L, McMilian JC, Bachy JL (1979) Tracheostomy and indwelling central venous line: a hazaradous combination? Intensive Care Med 5:83–86
38. Rijnders BJ, Peetermans WE, Verwaest C, Wilmer A, Van Wijngaerden E (2004) Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med 30:1073–1080
39. Falagas ME, Fragoulis K, Bliziotis JA, Chatzinikolau I (2007) Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 59:359–369