Central Venous Catheter-Related Bloodstream Infection Caused by *Staphylococcus aureus*: Microbiology and Risk Factors

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Although central vascular catheters (CVC) are indispensable in modern medicine, they are an important risk factor for primary bacteremias. We examined the incidence and risk factors associated with catheter-related bloodstream infection (CR-BSI) caused by *Staphylococcus aureus* in surgical patients. A prospective study was carried out in the Hospital das Clínicas da Universidade Federal de Uberlândia (HC-UFU) from September 2000 to December 2002. The skin insertion site, catheter tip, and blood were microbiologically analyzed. Demographics and risk factors were recorded for each patient, and cultures were identified phenotypically. *Staphylococcus aureus* was the most frequent pathogen, with an incidence rate of 4.9 episodes of CR-BSIs per 1,000 catheter/days. Based on logistic regression, the independent risk factors were: colonization on the insertion site =200 colony forming units (CFU)/20 cm^2 (p=0.03; odds ratio (OR) =6.89) and catheter tip (p=0.01; OR=7.95). The CR-BSI rate was high; it was mainly associated with *S. aureus*, and skin colonization at the insertion site and on the catheter tip were important risk factors for CR-BSI.

Key Words: *Staphylococcus aureus*, ventral venous catheter, bloodstream infection.

Safe vascular access is one of the key factors for modern medical practice; however, the intravascular devices (IVDs) needed for establishing reliable access are significantly associated with iatrogenic disease, especially bacteremia and candidemia [1,2]. Over 250,000 bloodstream infections (BSI) related to the presence of IVDs occur each year in the U.S., with an attributed death rate of 12-25%; BSIs also extend hospital internment, with additional costs of US$33,000-35,000/ patient [3,4]. Among IVDs, the use of central venous catheters (CVCs) is frequently followed by both local and systemic complications, including septic thrombophlebitis, endocarditis, metastatic infections, and bacteremias [5].

It is estimated that over 80% of all catheter-related bloodstream infections (CR-BSIs) are associated with CVCs, although they account for only a small percentage of all vascular catheters. CR-BSIs cause substantial morbidity and mortality, and they increase internment time and costs [6].

The pathogenesis of CR-BSI is multifactorial and complex. Although venous and arterial catheters may be colonized via the bloodstream from infections at other sites, through intestinal translocation or through administration of fluids (intrinsic contamination), available data suggest that most infections by staphylococci result from the migration of these microorganisms from the skin insertion site or from the catheter hub [7].

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According to the "US National Nosocomial Infections Surveillance System Report", the pathogens most frequently associated with CR-BSI etiology from 1991-1999 were: coagulase-negative *Staphylococcus* (CoNSs) (37%), *S. aureus* (13%), *Enterococcus* spp. (13%), and *Candida albicans* (8%)[8].

We evaluate the pathogenesis of primary *S. aureus* bacteremias in surgical patients who had undergone central venous catheterization, and we examined their respective risk factors.

Material and Methods

Study design. An observational prospective study was carried out through an active search system, based on spontaneous hospital demand, at Clinical Surgical Ward II of the Uberlândia Federal University Hospital (HC-UFU). Demographics, and intrinsic and extrinsic risk factors were recorded for each of the patients.

Microbiological techniques

CVC insertion site. The skin at the insert site of CVC was swabbed. Two samples were taken: the first, when the catheter was inserted and the second 5-7 days after insertion. Approximately 20 cm^2 of skin at the catheter insertion site was cleaned using sterile pre-moistened swabs. The swab was placed into an 1 mL tube with PBS + 0.1% of sodium thiosulphate, which agitated with a vortex, and about 0.1 mL of the fluid was inoculated on blood agar and mannitol salt plates. Skin cultures were considered positive whenever ≥200 UFC were isolated [9].

CVC tip. Catheters were removed under sterile conditions. The tips of the catheters were cut with sterile scissors and

transported to the laboratory in tubes containing 10 mL of phosphate-buffered saline (PBS) + 0.1% Tween 80. The cultures of the catheter tips were examined quantitatively, using a modified Brun-Buisson [10] technique; a segment of approximately 5 cm of the catheter tip was placed in a tube containing 10 mL of PBS + 0.1% Tween 80 and agitated in a vortex for 1 minute; 0.1 mL of the liquid was inoculated in agar blood, McConkey agar and mannitol salt agar plates and incubated at 37°C for 24 hours to determine the number of colony forming units (CFUs). Cultures were considered positive when $\geq 10^2$ CFU/mL were detected.

Hemocultures. Blood specimens were obtained through peripheral venous puncture. Hemocultures were performed by inoculating 5-10 mL of blood into a flask of the commercial automated system Bactec/Alert® (Vitek System, Organon Teknika Corp.). Positive culture flasks were sub-cultured in MacConkey agar and blood Agar, and plates were incubated at 37°C for 24-48 hours.

Bacterial identification. Clinical specimens obtained from skin at the insertion site of the central vascular catheter tip were identified by classical techniques, being initially separated into Gram-negative and Gram-positive bacilli, Gram-positive cocci and yeast-form fungi and afterwards by their morphological/staining characteristics. Gram-positive cocci were subjected to complementary tests: oxidase, catalase, growth in NaCl, coagulase, mannitol fermentation and DNAse for the identification of *S. aureus*, coagulase-negative *Staphylococcus* (CoNS) and other Gram-positive cocci. Blood cultures were obtained from the microbiology lab of HC-UFU.

Antimicrobial susceptibility tests

Disk diffusion agar technique. Samples were cultured in TSB medium at 37°C for 24 hours and then diluted in saline solution till the suspension opacity corresponded to the 0.5 tube of the MacFarland scale (1-2.10^8 CFU/mL); they were then seeded with a swab over the medium surface [11]. The following antimicrobial discs were used: amoxacillin-clavulanate, rifampin, clindamycin, cephalothin, tetracycline, sulfametoxazole-trimethoprim, ampicillin, ciprofloxacin, gentamicin, vancomycin, chloramphenicol, erythromycin, quinupristin-dalfopristin, linezolide, and oxacillin. A standard sample of *S. aureus* ATCC 25923 was used as a control for the susceptibility test.

CR-BSI definition. Catheter-related bloodstream infection (CR-BSI) were defined as isolation of the same microorganism (i.e. identical species and resistance) from a semiquantitative or quantitative culture of a catheter segment and from the blood (preferably drawn from a peripheral vein) of a patient with accompanying clinical symptoms and no other source of infection.

Statistical analysis

The statistical analysis of risk factors for infection and microbiological results were performed by applyaing the $\div^2$ test for comparing percentage values (qualitative variables) and the Fisher's exact test, when n was equal to or less than five. Risk factors and microbiological results were individually compared against a variable response (univariate analysis) with two by two contingency tables. Multivariate analysis through a logistic regression model were used for variables with high odds ratios. The Student's t-test was used for comparing means (quantitative variables). Statistical significance was defined as a p value less than 0.05. The analysis of variables was performed with statistical software SPSS PC version 11.0 (SPSS, Chicago) and Epi Info Software version 2000 (CDC Atlanta).

Results

Among 198 patients with a central vascular catheter inserted in the jugular vein (n=84) or a subclavia vein (n=114), 19 were withdrawn from the epidemiological analysis due non-recovery of catheter tips, removal to another unit, or hospital discharge, reducing the study to 179 patients. Four CR-BSIs caused by *S. aureus* were detected, another two were caused by MRSA. The CR-BSI rate caused by *S. aureus* was 4.9 episodes per 1,000 days/catheter and the CVCs colonization was 21.2%.

Risk factors analysis for catheter tip colonization are given Table 1. Evaluation by multivariate logistic regression analysis of risk factors associated with this contamination indicated the following: colonization at the CVC insertion site with $\geq$ 200 CFU/20 cm^2 skin, internment $\geq$14 days, catheterization $\geq$7days and presence of erythema (Table 2).

Risk factors significantly associated with a CR-BSI: insertion site included: $\geq$ 200 CFU/20 cm^2, $\geq 10^2$ CFU in the CVC tip, and presence of a multilumen catheter (Table 3). Based on the multivariate analysis, only bacteria at the insertion site ($p = 0.03$; OR = 6.89; confidence interval (CI) = 2.42-21.90) and in the tip ($p = 0.01$; OR = 7.95; CI = 1.95-19.60) were independent factors for CR-BSI (Table 4).

Microorganisms most frequently seen within SI, PC and blood are listed in Figure 1. The most frequent ones in SI were coagulase-negative *Staphylococcus* (49.7%) and *S. aureus* (31.2%), followed by *Enterococcus* (6.4%). In the microbiological analysis of the catheter tip, there was predominance of coagulase-negative *Staphylococcus* (60.5%) and *S. aureus* (28.9%), followed by Gram-negative bacilli (BGN) (7.9%). The frequency of isolates of *S. aureus* in the blood was greater than that of coagulase-negative *Staphylococcus* (41.4% *versus* 37.9%, respectively), followed by BGN (17.2%) and *Enterococcus* (3.5%). One hundred thirty-nine samples of *S. aureus* were isolated in these patients, 57 of which (41.0%) were MRSA and 82 (59.0%) MSSA. The

Table 1. Risk factors associated with central venous catheter tip colonization.

Risk factors	Catheter tip positive N=38	Catheter tip negative N=141	P (RR)
Dressing	2	14	0.52 (0.57)
≥200 CFU/20cm^2 at the insertion site	24	53	0.008 (2.27)
Age ≥ 60 years	23	67	0.21 (1.52)
Internment			
≥ 7 days	33	83	0.02 (3.58)
≥ 14 days	31	57	<0.01 (4.58)
Catheterization ≥ 7 days	38	65	<0.01 (NC)
Antimicrobial use	30	96	0.27 (1.58)
≥ 3 antimicrobials	15	20	0.001 (2.68)
Other invasive devices	37	131	0.46 (2.42)
≥3 devices	14	60	0.65 (0.83)
Hypoalbuminamia	14	58	0.77 (0.87)
Fever	24	53	0.008 (2.27)
Erythema	16	14	0.01 (3.61)
Mortality	05	07	0.14 (1.98)

Table 2. Independent risk factors for catheter tip colonization determined by multivariate logistic regression

Risk factors	P Value	Odds Ratio	Confidence interval
Insertion site ≥200 CFU/20cm^2	0.012	2.15	1.19-9.98
Internment ≥14 days	0.047	1.97	1.02-8.45
Catheterization ≥ 7 days	0.038	1.78	1.06-7.98
Erythema	0.022	2.14	2.01-13.61

Table 3. Risk factors associated with catheter-related bloodstream infection (CR-BSI) in surgical patients of the HC-UFU

Risk factors	CR-BSI		Pvalue (Relative Risk)
	Presence n=04	Absence n= 175	
Dressing	0	16	1.0 (NC*)
Insertion site ≥200 CFU/20cm^2	4	65	0.02 (NC)
Catheter tip ≥10^2 CFU	4	34	0.001 (NC)
Multilumen catheter	3	28	0.016 (14.32)
Age ≥ 60 years	1	89	0.36 (0.33)
Internment			
≥ 7 days	4	109	0.29 (NC)
≥ 14 days	3	85	0.36 (3.1)
Catheterization ≥ 7 days	4	99	0.13 (NC)
Antimicrobial use	*4*	*122*	*0.32 (NC)*
≥ 3 antimicrobials	2	33	0.17 (4.11)
Others invasive devices	4	164	1.0 (NC)
≥3 devices	3	71	0.30 (4.26)
Hypoalbuminamia	4	68	0.02 (NC)
Fever	4	73	0.03 (NC)
Erythema	2	28	0.13 (4.97)
Mortality	0	12	1.0 (NC)

*Not calculated.

Table 4. Independent risk factors associated with CR-BSI by multivariate logistic regression

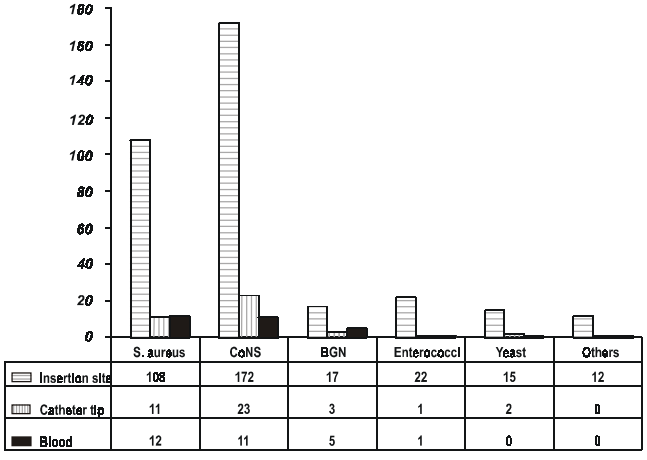
Risk Factors	P	Odds Ratio	CI
≥200 CFU/20cm^2 at the insertion site	0.03	6.89	2.42-21.90
Catheter tip ≥10^{2}CFU	0.01	7.95	1.95-19.60

CI = confidence interval.

Table 5. Antibiotic resistance patterns of MRSA and MSSA bacterial isolates from patients of the HC- UFU

Antimicrobials	MRSA n=57(%)	MSSA n=82(%)	P value
Ampicillin	54 (94.7)	57 (69.5)	<0.001
Amoxacillin-clavulanate	30 (52.6)	21 (25.9)	0.002
Cephalothin	44 (77.2)	21 (25.6)	<0.001
Ciprofloxacin	57 (100)	40 (48.7)	<0.001
Clindamycin	57 (100)	2.4 (2)	<0.001
Chloramphenicol	57 (100)	12.2 (10)	<0.001
Quinupristin-dalfopristin	0 (0)	0 (0)	1.0
Erythromycin	57 (100)	41 (50.0)	<0.001
Gentamicin	57 (100)	3.6 (3)	<0.001
Linezolide	0 (0)	0 (0)	1.0
Rifampin	57 (100)	7 (8.5)	<0.001
Sulfametoxazole-trimethoprim	57 (100)	7 (8.5)	<0.001
Tetracycline	48 (84.2)	10 (12.2)	<0.001
Vancomycin	0 (0)	0 (0)	1.0

Figure 1.



phenotype MRSA was responsible for 37.1% and 36.4% of colonies at the insertion site and in the catheter tip, respectively, and they accounted for 50% of the BSIs caused by *S. aureus*.

Among MRSA isolates, multiresistance was the most commonly observed pattern, with simultaneous resistance to clindamycin, chloramphenicol, erythromycin, gentamycin, rifampicin, sulfametoxazol-trimetoprim, and tetracycline. Among MSSA samples, resistance to ampicillin, erythromycin and ciprofloxacin were more frequent. All the samples of *S. aureus* (MRSA/MSSA) were susceptible to dalfopristin/quinupristin and linezolide, as well as to vancomycin (Table 5).

Discussion

The incidence of CR-BSI varies considerably with the type of catheter, but most (90.0%) are associated with the use of short-term, non-tunnel CVCs, inserted into the internal jugular vein and the subclavia vein [12], which are the veins that we analyzed. The proportion of CB-BSIs varies from 2.5% to 6.4% [13-16], with rates corresponding to 2.4-12.0 episodes per 1,000 days/CVC [17-22]. We found a rate of 2.2%, or 4.9 episodes per 1,000 days/catheter, among patients that were not in the intensive-care unit (ICU).

A series of studies published in the 90's investigating CVCs that were not soaked with antimicrobial antiseptic gave a variation of the colonization rate for these catheters of from 23.6% to 52.2% in patients in ICUs [14-16,23-25]. In our study the colonization rate of CVCs was lower (21.2%).

Risk Factors associated with CR-BSI are numerous; they can be divided into intrinsic and extrinsic factors, with the following highlights: surgical services, prolonged hospital internment, ICU care, active infection at another site, underweight premature born infant, difficulty in inserting the CVC, high APACHE score, site of CVC insertion (internal jugular/femoral veins), type of bandage, skin colonization at the pericatheter site, duration of catheterization (>7/10 days), colonization of the catheter cannon, parenteral feeding, among

others [22,26]. We found the following factors of risk to be significantly associated with CR-BSI: SI colonization ≥ 200 CFU/20 cm^2 and ≥ 10^3 CFU on the catheter tip.

Studies have shown that an important factor of risk associated with PC and cannon colonization, is colonization of the pericatheter cutaneous site [27,28]. This colonization proved to be an independent risk for factor PC colonization in our study, as were internment time greater than or equal to 14 days and catheterization over seven days.

In CVCs lasting for less than eight days, catheter colonization is more commonly (75% to 90%) a result of extralumen migration of skin microorganisms to the catheter tip inside the blood vessel [22]. Colonization at the insertion site of 6.5-56.5 results in a relative risk (RR) for CR-BSI [26]. This observation suggests that bandages applied at this site can have considerable influence on the incidence of these infections [29-31]. In most infirmaries and units of the HC-UFU non-use of frequent occlusive bandaging prevails in this invasive procedure. Only 16 patients (8.9%) had occlusive bandages and 87.5% of them had <200 CFU/20 cm^2 on the pericatheter skin.

Most of the microorganisms implied in CR-BSI are part of the normal skin microbiota. Gram-positive cocci are responsible for, at least two-thirds of these infections [32]. Coagulase-negative *Staphylococcus* (*Staphylococcus epidermidis*) is the most common agent, followed by *S. aureus, Enterococcus* spp., Gram-negative bacilli and yeast-form fungi [33]. However, in our study *S. aureus* was the most frequent pathogen (38%), surpassing CoNS (34.0% and BGN (24.0%).

In an overview published in 2002 [34] about a series of prospective studies performed in the 90s, CoNS were the most frequently isolated microorganisms on the catheter tip, different from the blood, where the *S. aureus* was the most frequent. More recent studies confirm these findings [28,35]. In our investigation, CoNs frequently colonized the tip was (60%), while *S. aureus* was found in 30%; in the blood we saw a higher percentage of *S. aureus* (38%). The prevalence of *S. aureus* over CoNS in the blood was also reported by other investigators [36-38].

The microbiological diagnosis of a CR-BSI is very important, because its therapy will vary according to the isolated agent and according to its resistance spectrum. CoNS result in lower mortality rates than *S. aureus*, BGN, and *Candida* spp.[39,40].

Another important aspect about these infections is resistance to antimicrobial drugs, since many CR-BSI agents are resistant to routinely-used antimicrobials. Oxacillin-resistant CoNS and *S. aureus* infections are growing in frequency, especially within tertiary and/or school hospitals; they account for over 30% of isolates in some Brazilian hospitals, 34% in North-American hospitals and about 1.8-54.0% in European countries [41,42]. Among CoNS samples, isolates resistant to penicillin reach rates up to 85.5%[43]. In a previous study carried out at the HC-UFU, we found a frequency of 44% samples resistant to oxacillin amongst *S. aureus* isolates [44], similar to the 41.0% that we now have found.

MSRA isolates are usually resistant to several antibiotics, including betalactamics, aminoglucosides, macrolides, fluoroquinolones, chloramphenicol, mupirocin, and others; vancomycin is the drug of choice for treating severe infections by these microorganisms [45]. Recently, two new drugs, dalfopristine/quinopristine and linezolide, appeared as options for treating infections caused by MRSA [46]. In our investigation, we found an association of resistance to oxacillin in MRSA isolates showing susceptibility to vancomycin, dalfopristine/quinopristine and linezolide.

The routes of contamination by staphylococci of the CVC tip, with subsequent CR-BSI, are extraluminal in those of short lasting (<8 days) and intraluminal in those of long lasting (>8 days) infections; the blood stream is the most probable route in critically ill patients, as previously described [47]. In our study, the presence of microorganisms at the CVC insertion site was an independent risk factor associated with CVC colonization, showing the importance of the skin as a reservoir of this microorganism for CVC-tip colonization. In CR-BSI pathogenesis, while *S. epidermidis* and other CoNS usually adhere to the surface of the CVC polymer to form slime/glycocalyx after catheter insertion into the vascular system, in *S. aureus* the main mechanism of invasion is mediated by protein adhesins on the bacterial cell wall, involving fibrinogenic receptors and fibronectine in the biofilm of the CVC tip [48].

In the pathogenesis of CR-BSIs caused by *S. aureus*, the importance of nasal contamination by this microorganism is well established [49,50]. Sesso et al. [51] showed that nasal decolonization reduces the risk of pericatheter colonization eight-fold and CR-BSI four-fold. Nasal colonization by *S. aureus* in patients enrolled in our study was not assessed as a predisposing factor for this infection, but the presence of ≥200 CFU/20 cm^2 at the CVC insertion site was an independent risk factor for CR-BSI (OR=6.89). The bacterial load on the CVC tip is related to CVC culture positivity, and to finding of bacteria in blood culture and therefore to CR-BSI [52]. In our study, considering only cases of sepsis by *S. aureus*, ≥ 10^2 CFU catheter tip colonization was a significant factor (OR=7.85), based on multiple logistic regression analysis.

The potential risk of not using occlusive bandages in the routine care of CVCs, which we found frequently in our investigation, also influences colonization levels at the CVC insertion site; it is associated with colonization on the catheter tip by *S. aureus*, an important factor in the pathogenesis of primary bacteremias.

References

1. Raad I. Intravascular catheter-related infections. The Lancet **1998**;351:893-8.
2. Mermel L.A. Prevention of intravascular catheter-related infections, Annals Internal Medicine **2000**;132:391-402.

3. Pitet D., Tarara D., Wenzel, R. Nosocomial bloodstream infection in critically ill patients: excess length of saty, extra costs, and atributable mortality. Journal American Medical Association **1993**;271:1598-1601.
4. Digiovine B., Chenoweth C., Watts C., Higgins M. The atributable mortality and costs of primary nosocomial bloodstream infections in intensive care unit. American Journal of Respiratory Critical Care Medicine **1999**;160:976-81.
5. Fratino G., Mazzola C., Buffa P., et al. Mechanical complications related to indwelling central venous catheter in pediatric hematology/oncology patients. Pediatric Hematology and Oncology **2001**;18:317-24.
6. Maki D.G. Infections due to infusion therapy. In: Bennett J.V., Brachman P.S.[eds.] Hospital Infections. Boston, MA: Little Brown and Co. **1998**;689-724.
7. Crump J.A., Collignom P.J. Intravascular Catheter-associated infections. European Journal Clinical of Infectious Diseases **2000**;19:1-8.
8. National Nosocomial Infections Surveillance (Nnis) System Report, Data Summary from January 1992-June 2001, issued August 2001. American Journal Infection Control **2000**;29:404-21.
9. Maki D.G., Ringer M.,Alvarado C.J. Prospective randomised trial of povidine-iodine, alcohol, and chlorexidine for prevention of infection associated with central venous and arterial catheters. Lancet **1991**;338:339-43.
10. Brun-Buisson C., Abrouk F., Legrand P., et al. Diagnosis of central venous catheter-related sepsis: Critical level of quantitative tip cultures. Archives Internal Medicine **1987**;147:873-7.
11. National Committee For Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests, v. 17, **1997**.
12. Kluger D., Maki D. The relative risk of intravascular device-related bloodstream infections with different types of intravascular devices in adults: a meta-analysis of 206 published studies. Infection Control Hospital Epidemiology **2000**;21:95-6.
13. Bach A., Schmidt H., Bottiger B., Vogel B. Retention of antibacterial activity and bacterial colonization of antiseptic-bonded central venous catheters. Journal Antimicrobial Chemotherapy **1996**;37:315–22.
14. Tennenberg S., Lieser M., Mccurdy B., et al. A prospective randomized trial of an antibiotic- and antiseptic-coated central venous catheter in the prevention of catheter-related infections. Archives Surgery **1997**;132:1348-51.
15. Heard S.O., Wagle M., Vijayakumar E. Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. Archives Internal Medicine **1998**;158:81-8.
16. Hannan M., Juste R.N., Umasanker S. Antiseptic-bonded central venous catheters and bacterial colonisation. Anaesthesia **1999**;54:868-72.
17. Barsic B., Beus I., Marton E., et al. Nosocomial infections in critically ill infectious disease patients: results of a 7-year focal surveillance. Infection **1999**;27:16-22.
18. Wallace W.C., Cinat M., Gornick W.B., et al. Nosocomial infections in the surgical intensive care unit: a difference between trauma and surgical patients. American Surgeon **1999**;.65:987-90.
19. Eggimann P., Harbarth S., Constantin M.N., et al. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet **2000**;355:1864-8.
20. Finkelstein R., Rabino G., Kassis I., Mahamid I. Device-associated, device-day infection rates in an Israeli adult general intensive care unit. Journal Hospital Infection **2000**;44:200-5.
21. Richards M.J., Edwards J.R., Culver D.H., Gaynes R.P. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infection Control Hospital Epidemiology **2000**;21:510–5.
22. Sheretz J.R. Pathogenesis of vascular catheter infection, p. 111-125. *In* F.A. Waldvogel, A.L. Bisno (eds). Infections Associated with Indewelling Medical Devices. 3rd ed. ASM Press, Washington, D.C. **2000**.
23. Loo S., Van Heerden P.V., Gollege C.L., et al. Infection in central lines: antisepticimpregnated *versus* standard non-impregnated catheters. Anaesthesia Intensive Care **1997**;25:637-9.
24. Maki D.G., Stolz S.M., Wheeler S., Mermel L.A. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. Annals Internal Medicine **1997**;127:257-66.
25. Marik P.E., Abraham G., Careau P., et al. The ex vivo antimicrobial activity and colonization rate of two antimicrobial-bonded central venous catheters. Critical Care Medicine **1999**;27:1128–31.
26. Safdar N., Kluger D.M., Maki D.G. A review of risk actors for CR-BSI caused by percytaveaously inserted, noncuffed central venous catheter. Medicine **2002**;81:466-79.
27. Egebo K., Toft P., Jakobsen C.J. Contamination of central venous catheters. The skin insertion site wound is a major source of contamination. Journal Hospital Infection **1996**;32:99-104.
28. Mahieu L.M., Dedooy J.J., Muynck A.O., et al. Microbiology na drisk factors for catheter exit-ste and –hub colonization in neonatal intensive care unit patients. Infection control Hospital Epidemiology **2001**;22:357-62.
29. Engervall P., Ringertz S., Hagman E., et al. Change of central venous catheter dressings twice a week is superior to once a week in patients with haematological malignancies. Journal Hospital Infection **1995**;29:275-86.
30. Nikoletti S., Leslie G., Gandossi S., et al. A prospective, randomized, controlled trial comparing transparent polyurethane and hydrocolloid dressings for central venous catheters. American Journal Infection Control **1999**;27:488-96.
31. Curchoe R.M., Powers J., El-Daher N. Weekly transparent dressing changes linked to increased bacteremia rates. Infection Control Hospital Epidemiology **2002**;23:730-2.
32. Darouiche R.O., Raad I.I., Heard S.O., Mayhall G. A comparison of two antimicrobial-impregnated central venous catheters. New England Journal Medicine **1999**;340:1-8.
33. Centers For Disease Control And Prevention. *Staphylococcus aureus* resistant to Vancomycin - US. MMWR **2000**;48:1165-7.
34. Raad I.I., Hanna H.A. Intravascular catheter-related infections. Archives Internal Medicine **2002**;162:871-8.
35. Dobbins B.M., Kite P., Kindon A., et al. DNA fingerprinting analysis of coagulase negative staphylococci implicated in catheter related bloodstream infections. Journal Clinical Pathology **2000**;55:824-8.

36. Bantar C., Bustos J.L., Vesco E., Morera G. Central venous catheter-related infection: A prospective, observational study to assess the incidence rate at a teaching hospital in Argentina. Infection Control Hospital Epidemiology **2002**;23:757-8.
37. Richards B., Chaboyer W., Bladen T., Schluter P.J. Effect of central venous catheter type on infections: a prospective clinical trial. Journal Hospital Infection **2003**;54:10-7.
38. Öncü S., Özsüt H.,Yldirim Y., et al. Central venous catheter related infections: Risk factors and the effect of glycopeptide antibiotics. Annals of Clinical Microbiology and Antimicrobials **2003**;2:1-6.
39. Valles J., Leon C., Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). Clinical Infectiuos Diseases **1997**;24:387-95.
40. Rello J. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. Am J Respir Crit Care Méd **2000**;162:1027-30.
41. Moreira M., Medeiros E.A.S., Pignatari A.C.C., et al. Efeito da infecção hospitalar da corrente sanguínea por *Staphylococcus aureus* resistente à oxacilina sobre a letalidade e o tempo de hospitalização. Revista Associação Médica Brasileira **1998**;44:263-8.
42. Diekema D.J., Pfaller M.A., Jones R.N., et al. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific Region for the SENTRY antimicrobial Surveillance Program, 1997-1999. Clinical Infectious Diseases **2001**;02:S114-32.
43. Frebourg N.B., Cauliez B., Lemeland J.F. Evidence for nasal carriage of methicillin-resistant staphylococci colonizing intravascular devices. Journal of Clinical Microbiology **1999**;37:1182-5.
44. Sadoyama G., Gontijo Filho P.P. Risk factors for methicillin-resistant and sensitive Staphylococcus aureus in a Brazilian university hospital. Braz J Infect Dis **2000**;4:135-43.
45. Chambers H.F. Methicillin Resistance in Staphylococci: Molecular and Biochemical Basis and Clinical Implications. Clinical Microbiology Reviews **1997**;10:781-91.
46. Bhavnani S.M., Ballow C.H. New agents for Gram-positive bacteria. Current Opinion in Microbiology **2000**;03:528-34.
47. Crnich C.J., Maki D.G. The promise of novel technology for the prevention of intravascular device-related bloodstream infection. Pathogenesis and short-term devices. Clinical Infectious Diseases **2002**;34:1232-42.
48. Eiff C.V., Peters G., Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infectious Diseases **2002**;02:677-85.
49. Kluytmans J., Belkum A.V., Verbrugh H. Nasal Carriage of *Staphylococcus aureus*: Epidemiology, Underlying Mechanisms, and Associated Risks. Clinical microbiology reviews **1997**;10:505-20.
50. Livesly M.A., Tebbs S.E., Moss M.A., et al. Use pulsed field gel eletrophoresis to determine the source of microbial contamination of central venous catheters. European Journal Clinical Infectious Diseases **1998**;17:108-12.
51. Sesso R., Barbosa D., Leme I.L., et al. *Staphylococcus aureus* prophylaxis in hemodialysis patients during central venous catheters: effect of mupirocin ointment. Journal Medical Society Neprhology **1998**;09:1085-92.
52. Rijnders B.J.A., Wijngaerden E.V., Peetermans W.E. Catheter-tip colonization as a surrogate end point clinical studies on catheter-related bloodstream infection: How strong is the evidence? Clinical Infectious Diseases **2002**;35:1053-8.