Risk Factors for Central Venous Catheter-Related Infections in Surgical and Intensive Care Units

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RISK FACTORS FOR CENTRAL VENOUS CATHETER-RELATED INFECTIONS IN SURGICAL AND INTENSIVE CARE UNITS

Maria Luisa Moro, MD; Egidio Franco Viganò, MD; Alessandro Cozzi Lepri, MD; The Central Venous Catheter-Related Infections Study Group

ABSTRACT

OBJECTIVE: To identify avoidable risk factors for central venous catheter (CVC) infections in patients undergoing short-term catheterization.

DESIGN: Prospective multicenter cohort study.

SETTING: Two university teaching hospitals and five large nonteaching hospitals.

PATIENTS: Patients admitted to intensive care units or surgical units and exposed to short-term CVCs.

RESULTS: Of 623 catheterization episodes, 9.3% were associated with catheter-related infections (CRI). The skin at the catheter site was frequently colonized (16.2%) and was the potential source of infection in 56.1% of the cases, mostly local infections. The hub was colonized less frequently (3.5%) but was responsible for systemic infections more frequently.

The following variables were independently associated with CRI: duration of catheterization (for 7 to 14 days, odds ratio [OR], 3.9; 95% confidence interval $[CI]_{95}$, 1.4 to 10.7; and for >14 days, OR, 5.1; CI_{95}, 1.7 to 15.4), coronary care unit service (OR, 6.7; CI_{95}, 1.1 to 42.9) or surgery service (OR, 4.4; CI_{95}, 1.03 to 18.5), second episode of catheterization (OR, 7.6; CI_{95}, 1.8 to 32.3), skin colonization at the insertion site (OR, 56.5; CI_{95}, 10.8 to 296), and hub colonization (OR, 17.9; CI_{95}, 2.4 to 132).

The risk associated with skin colonization varied with use of jugular access or simultaneous colonization of the hub. When only symptomatic CRI was considered, the risk associated with hub colonization was consistently higher (OR, 36.6; CI_{95}, 7 to 190) than that associated with skin colonization (OR, 3.2; CI_{95}, 0.7 to 14).

Age, transparent dressing, jugular insertion, male gender, duration of catheterization, and hub colonization were independent risk factors for skin colonization. The effect of age varied by type of dressing and vice versa; the effect of jugular access varied by sex; and the effect of transparent dressing varied by length of catheterization and vice versa.

Total parenteral nutrition and skin colonization were independently associated with an increased risk of hub colonization.

CONCLUSIONS: Skin and hub colonization are the two major determinants for endemic CRIs; colonization of the hub, however, is more frequently associated with more severe infections. In order to reduce CRIs, more efforts should be focused on understanding which factors increase the risk of colonization both of the skin and of the hub (*Infect Control Hosp Epidemiol* 1994; 15:253-264).

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INTRODUCTION

Infection constitutes a potentially life-threatening complication of central venous catheterization. The reported incidence of catheter-related septicemia for short-term, noncuffed, central venous catheters is in the range of 3% to 5%, which is much higher than that reported for peripheral intravenous catheters.[1]

Central venous catheters (CVCs) have gained widespread use in hospitals, especially in intensive care units (ICUs), surgical units, and hemodialysis units. As a consequence, the size of the population at risk for acquiring a catheter-related bacteremia has increased, which may explain partially the observed increasing trend in the incidence of primary bacteremia in the last ten years.[2]

Knowledge of the pathogenesis and epidemiology of CVC-related infections has increased consistently over the last few years.[1,3,4] Several preventive measures aimed at reducing the risk of contamination of the percutaneous device or of the infusate administrated through the device have been proven to be effective. Nevertheless, the role played by specific factors in increasing the risk of infection still is not entirely clear, such as site of insertion, multilumen catheters, transparent dressings, etc.[5-7] We carried out a prospective multicenter study among hospital patients exposed to nonimplantable short-term CVCs in order to estimate the incidence of infectious complications and investigate potential risk factors for catheter-related infections (CRIs).

METHODS

Study Population

The study was conducted from February to October 1991 in seven Italian hospitals and included all patients who underwent central venous catheterization in ICUs or surgical units during the study period, except those with implantable catheters used for long-term intravascular therapy (ie, Hickman and Broviac catheters). Most ICUs in Italy are mixed medical/surgical units that deliver critical care for a variety of clinical conditions except cardiovascular diseases, which generally are cared for in specialized units. The ICUs participating in the study were all general mixed medical/surgical units (referred to as ICUs in this article), specialized medical units for coronary care (CCUs) or specialized cardiac surgery units (CSUs).

Protocol for Catheter Care

A common protocol for catheter care was adopted by the participating units. The following practices were recommended: 1) use of central venous access only when absolutely necessary; 2) removal and reinsertion of CVCs inserted in emergency; 3) aseptic technique for insertion (sterile gloves, drapes, gowns, face mask, surgical scrubbing with povidone-iodine or chlorhexidine); 4) site preparation: skin cleansing with water and soap and disinfection of the skin with 1% to 2% tincture of iodine, with 10% povidone-iodine, or with a solution of 0.5% clorhexidine in 70% alcohol for 2 minutes; 5) no use of antimicrobial ointment; 6) covering of the site with sterile gauze or with an occlusive transparent dressing; 7) daily inspection of the catheter site; 8) dressing changes every 48 to 72 hours when gauze dressings were used; 9) IV set changes every 48 to 72 hours; 10) no blood drawing through the catheter; 11) before any manipulation of the catheter, handwashing with an antiseptic and disinfection of the catheter entry port with povidone-iodine were required. Compliance with the recommended practices was not audited.

Data Collection

We followed each patient from catheter insertion to removal and collected data on patient-related factors (ie, age, underlying disease, and presence of a distant infection) and on patient-care practices (ie, reasons for catheter usage, difficulties in insertion, where insertion was performed, insertion site, number of catheter lumens, type of catheter dressing, duration of catheterization, and catheter exchange over a guidewire). Information on the number of manipulations of the hub was not collected, but the reason for catheterization was used as an indirect measure for this variable, assuming that patients receiving total parenteral nutrition (TPN) or with hemodynamic monitoring were exposed to a higher number of hub manipulations than patients for whom the CVC was used for administration of fluids only.

An episode of catheterization was defined as the time from insertion of the catheter in a specific site to its removal. A catheter that was exchanged and immediately substituted with a new catheter in the same entry site was considered as part of the same catheterization episode. A new catheter inserted in a different site or in the same site but after a 24-hour interval was considered as part of a new catheterization episode.

A study nurse in charge in each participating ward evaluated each patient daily, inspecting the insertion site for signs of inflammation whenever the dressing was changed or the catheter was removed. Peripheral blood cultures were taken from patients with fever or other signs of infection. Catheters were removed aseptically and cultures were obtained. Swabs were taken immediately from the site of catheter insertion and from the hub.

Microbiological Methods

Catheters were removed after decontamination

of the insertion site with povidone-iodine. The catheter tip was cut with sterile scissors and transported to the laboratory in sterile tubes. Catheter cultures were obtained semiquantitatively, as described by Maki et al,[8] or quantitatively, using a modified Cleri technique[9]: a 5-cm segment of the catheter tip was placed in 5 mL of tryptose broth and waved for 1 minute with vortex; 0.1 mL of the broth was then streaked onto a TSA agar plate + 5% sheep blood and incubated for 48 hours at 35°C. Cultures were considered positive if >15 cfu (Maki technique) or >1,000 cfu (modified Cleri technique) were isolated. Of the 630 catheter tips examined, 30% were analyzed using the Maki technique and 70% were analyzed with the modified Cleri technique.

An approximate 20-cm^2 area of skin at the site of catheter insertion was swabbed using sterile premoistened swabs. Each swab then was inoculated onto a blood agar plate, and a quantitative culture was obtained. The skin culture was considered positive if >200 cfu were isolated. The method for skin sampling and the cutoff point of 200 cfu were taken from Maki,[10] who found that baseline skin cultures at central venous catheter insertion were about 200 cfu for 20-cm^2 sampling. No validation of the method for skin sampling has been carried out.

Cultures of the catheter hubs also were obtained by sterile premoistened swabs inserted into the hub and gently rubbed. Each swab then was inoculated onto blood agar plate. The culture was considered positive if >100 cfu were isolated. The cutoff point of 100 cfu was taken from Fan,[11] who found that in CRIs quantitative cultures of the hub were always >100 cfu, while lower bacterial growths were found in contaminated catheters.

Colony counts for both skin and hub refer to the dominant species of microorganism. Coagulase-negative staphylococci were speciated in two thirds of the cases. No isolates were typed further than to species level.

Definitions

Catheter-related infections were defined as follows:

Local Infections of the Catheter Site. 1) Isolation of a significant number of microorganisms (see above) on semiquantitative or quantitative culture, whether inflammation of the catheter site was present or not; or 2) presence of purulent drainage at the vascular site.

Catheter-Related Septicemia. a) Isolation of a significant number of the same species of microorganism (see above) on semiquantitative or quantitative culture of the catheter and from blood cultures obtained by separate venipuncture; b) no apparent source of the bacteremia or fungemia; and c) clinical features consistent with bloodstream infection (fever >38°C, chills, hypotension, or oliguria <20 cc/hr with no other recognized cause).

Catheter-Related Bacteremia. Isolation of a significant number (see above) of the same species of microorganism on semiquantitative or quantitative culture of the catheter and from blood cultures obtained by separate venipuncture, in the absence of systemic signs of infection.[12]

The skin at the insertion site was considered as the potential source of a catheter-related infection if the same species of microorganism was isolated from both the catheter tip and the skin. If the same species was isolated from the catheter tip and from the hub, the infection was considered potentially due to the hub. Both the skin and the hub were considered as sources of infection if the same species was isolated from the catheter tip, the skin, and the hub. For the one third of coagulase-negative staphylococci not speciated, the concordance among microorganisms isolated from skin, hub, and catheter tips was judged on the concomitant presence of CNS and on the basis of concordance of antimicrobial susceptibilities of microorganisms performed using standard procedures or an automated system.

Statistical Methods

Data were analyzed using the BMDP statistical package.[13] Odds ratios (ORs) and Pearson chi-square tests were calculated to identify which factors were most related to outcome. A multiple logistic regression using the BMDPLR program then was performed to obtain an adjusted estimate of the ORs and to identify which factors were associated independently with CRI. All variables that showed a P value below 0.25 in the univariate analysis were entered into the model.

A significant improvement in the log-likelihood function was the main criterion for entering variables in the model. The effect of possible confounding factors was verified by introducing them in the final model and noting the change in the coefficients of the risk factors. The existence of plausible first-order interactions between the variables that entered the final model also was verified. This test was carried out using as criteria either a significant improvement in the log-likelihood function or a significant value of the Wald statistic associated with the interaction term.[14] Given that skin and hub colonization represent intermediate steps in the causal chain of catheter-related infections, we separately analyzed risk factors for catheter-related infections, skin colonization, and hub colonization, building three separate logistic models, each using one of the three previously mentioned outcome measures.

Regarding analysis aimed at evaluating risk fac-

TABLE 1
CHARACTERISTICS OF THE STUDY POPULATION AND OF THE EPISODES OF CATHETERIZATION

Characteristics	
No. of patients studied	607
Mean age (years)	61.0
(SD, range)	(15.7, 4 to 91)
Sex, male (%)	66.5
Primary diagnosis (%)	
Cancer	30.5
Cardiovascular disease	37.7
Gastrointestinal disease	14.3
Trauma	8.8
Other	8.7
Presence of other diagnoses (%)	34.6
Service (%)	
General intensive care	18.4
Cardiac intensive care	28.5
Surgery	53.1
No. of episodes of catheterization	623
Purpose of catheter	
Total parenteral nutrition (TPN)	26.9
Hemodynamic monitoring (HM)	28.9
TPN and HM	20.6
Administration of fluids	19.7
Other	3.9
Duration of catheterization (days)	
Mean (SD, range)	
First episode	8.5 (7.8, 1 to 65)
Second episode	12.8 (11.8, 1 to 49)

tors, we did not include the 156 catheterization episodes for which one or more variables were missing. Of these episodes, 77.6% were observed in two surgical wards of two different hospitals, where a low incidence of catheter complications was recorded. The incidence of infections observed in the 156 excluded catheters was 3.8%, compared with 11.1% in the 467 catheterization episodes included in the analysis of risk factors. In order to determine whether the results of the risk factor analysis were affected by selection of a particular subgroup of cases, further analysis was conducted. Using the same model-building strategy described above, a logistic regression for catheter infection was applied to the 618 cases for whom variables found to be relevant for the 467 cases had been accurately recorded. This model did not differ either in terms of variables included or ORs.

RESULTS

Characteristics of the Study Population

We observed 623 episodes of central venous catheterization among 607 patients. More than half of the studied patients were hospitalized in surgical units, and a catheter was used in 76% of the cases for TPN, hemodynamic monitoring, or both. The first episode of catheterization lasted, on average, 4 days less than the second episode (Table 1).

Catheter-Related Infections and Potential Infection Sources

Overall, 58 CRIs were recorded (9.3/100 catheters): 47 were local infections (7.5/100 catheters) and 11 were septicemias (1.8/100). One patient developed both local CRI and catheter-related septicemia; no catheter-related bacteremia in the absence of systemic signs of infection was observed. Twenty patients (3.2/100) developed a septicemia unrelated to the catheter. In three cases, the sepsis was secondary to other sources of infection; in 17 patients the catheter tip was not colonized.

The incidence of CRI was higher in surgical units (13.3/100 catheterization; 1.4/100 catheter-days), followed by CSUs (5.7/100 catheterizations; 1.4/100 catheter-days), CCUs (4.8/100 catheterizations; 1.0/100 catheter-days), and ICUs (4.1/100 catheterizations; 0.32/100 catheter-days). More than half (56.3%) of the microorganisms responsible for CRI were coagulase-negative staphylococci (CNS); (*Staphylococcus epidermidis* was isolated in 24 cases, while in the other 12 cases CNSs were not speciated), 7.8% were gram-negative bacilli, 12.5% were *Candida* species, and 23.4% were other microorganisms. Catheter-tip colonization with *Candida* species was frequently associated with systemic infections (Table 2).

At catheter removal, the skin was colonized in 98 patients (16.2%) and the hub in 21 patients (3.5%). The same species of microorganism was isolated from the skin and from the catheter tip in 27 CRIs, 26 of which were local infections. The hub was implicated as the potential source of infection for three infections, all systemic; both the skin and the hub were colonized with the same species of microorganism isolated from the catheter tip in five infections: two local and three systemic. In 22 (38.6%) of 57 CRIs, the skin and/or hub were not colonized or the microorganism isolated from the catheter tip was different (Table 3).

Thirty-two microorganisms were isolated in skin-related infections, three in hub-related infections, and six in infections related to both skin and the hub. Of the microorganisms responsible for skin-related infections, 28 (87.5%) were gram-positive (mainly coagulase-negative staphylococci), two were gram-negative, and two were *Candida albicans.* The three infections that potentially originated from the hub were due to *Candida tropicalis, Pseudomonas aeruginosa,* and *Staphylococcus epidermidis.* Of the six microorganisms iso-

TABLE 2
MICROORGANISMS ISOLATED FROM CATHETER-TIP CULTURES, CLASSIFIED BY TYPE OF INFECTION

	Catheter-Related Infections					
	Local		Septicemias		Total	
Organism	**No.**	**%**	**No.**	**%**	**No.**	**%**
Staphylococcus epidermidis	22	43.1	2	14.3	24	36.9
Unspeciated coagulase-negative staphylococci	11	21.6	1	7.1	12	18.5
Staphylococcus aureus	7	13.7	1	7.1	8	12.3
Other gram-positive	5	9.8	3	21.5	8	12.3
Klebsiella oxytoca	1	2.0	1	7.1	2	3.1
Enterobacter cloacae	1	2.0	0	0.0	1	1.5
Proteus mirabilis	1	2.0	0	0.0	1	1.5
Pseudomonas aeruginosa	0	0.0	1	7.1	1	1.5
Candida albicans	3	5.9	4	28.7	7	10.8
Candida tropicalis	0	0.0	1	7.1	1	1.5
Total	51	100.0	14	100.0	65	100.0

The culture of the catheter tip was positive in 56 patients (one local infection was diagnosed on the presence of purulent drainage only and in one patient both a local and a systemic infection were detected, involving the same microorganism) in 49 infections 1 microorganism was isolated, and in 8 infections 2 microorganisms.

lated from patients for whom both the skin and the hub were positive, five were staphylococci and one was *Candida albicans.*

RISK FACTORS

Catheter Infections

Table 4 shows the univariate analysis of risk factors associated with CRI. Duration of catheterization, admission to coronary care/cardiosurgical units (CCU) or to surgical units, jugular insertion, transparent dressing, TPN, second catheterization episode and, above all, skin colonization and hub colonization showed significant associations with catheter infections. Age, sex, place of catheter insertion (ie, wards/operating room), difficult insertion, number of catheter lumens, urgent/elective insertion, and catheter exchange (over a guidewire or not) were not associated with catheter infections.

The independent risk factors predictive of catheter-related infections obtained in the logistic regression analysis are shown in Table 5. Only TPN and type of dressing were no longer significantly associated with catheter infection after adjustment with logistic analysis. The risk of infection increased with increasing duration of exposure (OR, 3.9 for 7 to 14 days; OR, 5.1 for >14 days); the infection risk both for patients staying in CCUs and in surgical units was approximately six times greater than that of patients admitted to ICUs; the probability of developing a catheter infection was seven times higher during the second episode of catheterization. We detected the existence of interactions between skin colonization and hub colonization and between skin colonization and jugular site. The risk

TABLE 3
POTENTIAL SOURCES OF CATHETER-RELATED INFECTIONS

	Local Infections		Septicemias	
Potential Source	**No.**	**%**	**No.**	**%**
Colonization of skin at the insertion site	26	55.3	1	9.1
Contamination of hub	0	0.0	3	27.3
Skin and hub	2	4.3	3	27.3
Unknown	19	40.4	4	36.3
Total	47	100.0	11	100.0

associated with skin colonization varied considerably among patients with different levels of the other two variables: skin colonization represented the greatest risk factor for catheter infections when the hub was not colonized or when the jugular insertion was not used (OR, 56.5; CI_{95}, 10.8 to 296); the risk independently associated with skin colonization decreased to 8.8 when the catheter was inserted through the jugular vein, and it was no longer statistically significant when the hub was colonized simultaneously.

Accordingly, the independent effect of hub colonization was strong and statistically significant only when the skin was not colonized simultaneously (OR, 17.9; CI_{95}, 2.42 to 132). Jugular insertion resulted in a three times greater risk when the skin was not colonized; however, this difference was not statistically significant.

Among the 467 catheters included in this analysis, only 13 were associated with a symptomatic CRI,

TABLE 4
RISK FACTORS FOR CATHETER-RELATED INFECTIONS: UNIVARIATE ANALYSIS

Risk Factor	No. of Patients	Incidence/100	Unadjusted Odds Ratio	*P* Value
Duration of catheterization (days)				
≤7	211	4.3	1.0	
7 to 14	176	15.3	3.6	0.0004
>14	80	20.0	4.7	0.0009
Service				
ICU*	101	4.0	1.0	
CCU†	108	5.6	1.4	0.42
Surgery	258	16.3	4.1	0.003
Site of insertion jugular				
No	254	4.3	1.0	
Yes	213	19.2	4.5	0.00001
Type of dressing				
Regular	380	8.9	1.0	
Transparent	87	20.7	2.3	<0.0017
Total parenteral nutrition				
No	208	7.7	1.0	
Yes	259	13.9	1.8	0.034
2nd catheterization episode				
No	441	10.4	1.0	
Yes	26	23.1	2.2	0.046
Skin colonization				
No	381	4.2	1.0	
Yes	86	41.9	10.0	0.00001
Hub colonization				
No	447	9.2	1.0	
Yes	20	55.0	6.0	0.00001

* Intensive care units
† Coronary care/cardiosurgical units

of which 10 were septicemias. When only symptomatic CRIs were considered as the outcome measure in a logistic regression model, the OR for colonization of the hub was equal to 36.6 (CI_{95}, 7.04 to 190), while the OR for skin colonization was much lower: 3.15 (CI_{95}, 0.72 to 13.8).

Skin Colonization

In the univariate analysis, several factors appeared to be associated with skin colonization: age, duration of catheterization, stay in surgery, jugular insertion, transparent dressing, insertion in the operating room, urgent insertion, and hub colonization (Table 6). After adjustment, type of service, where insertion was performed, and urgent insertion were no longer associated significantly with colonization of the skin (Table 7). Hub colonization increased the probability of skin colonization by 25 times. The effect of age varied by type of dressing: the risk of skin colonization increased with increasing age (53 to 71 years: OR, 5.7; CI_{95}, 1.4 to 23.1; >71 years: OR, 13.4; CI_{95}, 3.1 to 57.0), but only when a gauze dressing was used. When an occlusive dressing was used, age alone was no longer a significant risk factor. However, use of transparent dressing increased the risk of skin colonization by 13 times in the younger subgroup of patients when the duration of catheterization was longer than 1 week. The risk associated with jugular insertion was greater for males (4.19 for females versus 29.3 for males); male gender was a risk factor for skin colonization only in cases of jugular insertion. Duration of catheterization longer than 7 days was a risk factor only when transparent dressing was used (OR, 5.39; CI_{95}, 2.9 to 9.89).

Hub Colonization

Several factors appeared to be associated with hub colonization in the univariate analysis (Table 8). After adjustment in the logistic regression analysis, only two factors appeared to be significant risk factors

for hub colonization: TPN (OR, 5.72; CI_{95}, 1.08 to 30.3), and skin colonization (OR, 22.1; CI_{95}, 5.96 to 81.9).

Given that hub colonization and skin colonization were highly correlated, we built two additional models for skin colonization excluding hub as a covariate, and for hub colonization excluding skin as a covariate. No additional factor, apart from those already considered, entered in the two models, showing that other factors have not been replaced and obscured by the presence of these two powerful variables.

TABLE 5
INDEPENDENT RISK FACTORS FOR CATHETER-RELATED INFECTIONS

Risk Factor	Odds Ratio	CI_{95}
Duration of catheterization (days)		
7 to 14	3.88	1.4 to 10.7
>14	5.07	1.7 to 15.4
Service		
CCU	6.73	1.1 to 42.9
Surgery	4.38	1.03 to 18.5
2nd catheterization episode	7.60	1.8 to 32.3
Skin colonization		
Hub negative/no jugular insertion	56.50	10.8 to 296.0
Hub negative/jugular insertion	8.79	3.83 to 20.17
Hub positive/no jugular insertion	4.70	0.39 to 56.6
Hub positive/jugular insertion	0.73	0.11 to 4.70
Hub colonization		
Skin negative	17.9	2.42 to 132.0
Skin positive	1.48	0.42 to 5.13
Jugular insertion		
Skin negative	3.03	0.88 to 10.4
Skin positive	0.47	0.1 to 2.2

DISCUSSION

More than 90% of all intravascular device-related bacteremias result from the use of central venous catheters.[15] Hence, a clear understanding of the pathogenesis of CRIs, as well as of which factors are associated with the greatest increase in the infection risk, is essential for developing effective prevention strategies. Several factors have been found to be associated with an increased CRI risk; however, some of the evidence is still conflicting, partly due to the fact that less recent studies have not applied analysis techniques capable of adjusting for potential confounding factors. Moreover, while skin colonization is a well-recognized risk factor for catheter-related infections, hub colonization has been overlooked frequently as an important source of infection.

In this study, we have estimated the independent risk associated with both skin and hub colonization and their association with severity of catheter-related infections, pointing out that hub colonization increases the risk of symptomatic CRI by 36 times. Moreover, we have assessed the major determinants for colonization of these two sites in a large multicenter trial involving different hospital settings.

The incidence of local and systemic infections observed in our prospective study (7.5/100 and 1.8/100, respectively) was in the range of that of studies published in the last decade. Specifically, the rate reported in the literature ranges from 3% to 5% when catheters are used for hemodynamic monitoring or hemodialysis, while the risk is lower, ranging from 1 to 2%, for catheters used for drug therapy or TPN outside an ICU[1]; more than half of the catheters included in our study belonged to the latter category. As in other studies, the predominant pathogens were coagulase-negative staphylococci, *Staphylococcus aureus,* and *Candida* species.[16-18] In 61.4% of the 57 catheter-related infections, we observed concordance between organisms colonizing the catheter and organisms colonizing the skin and/or the hub. The skin frequently was identified as a potential source of infection (56.1%) and was mainly responsible for local infections (28/32 infections). Colonization of the hub less frequently was found to be the source of infection (14.0%) but more frequently was associated with systemic infections (6/8). These results are similar to those reported by Maki, who studied 234 CVCs and observed that 2 of the 6 infections originating from the hub were systemic versus 6 of the 36 that originated from the skin.[19] Our results are limited by the fact that only two thirds of CNS were speciated: isolation of CNS both in superficial cultures and on the catheter, in fact, does not prove definitively that the isolated microorganisms were the same, due to the lack of species identification for one third of CNS. Moreover, microorganisms were not subtyped in order to accurately assess commonality among strains, as done by Mermel on Swan-Ganz catheters.[20] As shown by Widmer,[21] *Staphylococcus epidermidis* isolated from skin and catheter cultures in some instances can be proved to be different microorganisms after using restriction endonuclease plasmid analysis. Therefore, in our study, the source of infection could have been misclassified for some patients.

No agreement exists in the literature regarding the best method for assessing skin and hub colonization. A variety of methods have been proposed; the validity of the two most commonly used methods for skin sampling (swabs and Rodac plates) has been questioned recently and it has been suggested that a

TABLE 6
RISK FACTORS FOR SKIN COLONIZATION: UNIVARIATE ANALYSIS

Risk Factor	No. of Patients	Incidence/100	Unadjusted Odds Ratio	*P* Value
Age (years)				
≤53	100	10.0	1.0	
53 to 71	229	18.3	2.0	0.06
>71	138	24.6	2.9	0.005
Sex				
Female	165	15.2	1.0	
Male	302	20.2	1.4	0.18
Duration of catheterization (days)				
≤7	211	12.8	1.0	
7 to 14	176	21.6	1.9	0.02
>14	80	26.2	2.4	0.007
Service				
CCU*	108	6.5	1.0	
ICU†	101	7.9	1.2	n.s.
Surgery	258	27.5	5.5	0.00004
Site of insertion jugular				
No	254	4.7	1.0	
Yes	213	34.7	10.8	0.00003
Type of dressing				
Regular	380	14.7	1.0	
Transparent	87	34.5	3.0	0.00001
Place of insertion				
Ward	347	15.6	1.0	
Operating room	120	26.7	1.97	0.007
Insertion				
Elective	134	11.9	1.0	
Urgent	333	21.0	1.96	0.022
Hub colonization				
No	447	15.9	1.0	
Yes	20	75.0	15.9	0.00001

* Coronary care/cardiosurgical units
† Intensive care units

pad method could provide more accurate results.[22] The swab method, used in our study, seems to have a low sensitivity and efficiency, leading to a higher proportion of false-negatives. Moreover, no agreement exists on the cutoff points to be used to classify positive and negative skin and hub cultures, and a variety of different cutoff points have been adopted by different authors.[10,19,23,24] We adopted a rather conservative approach in order to reduce the proportion of false-positives (ie, skin and hub colonization not truly involved in the pathogenesis of the CRI observed). Given the low sensitivity of the method adopted for skin sampling and the high cutoff points chosen, we could have misclassified some skin and hub colonized patients as false-negatives; however, the effect of this misclassification is likely to be an underestimation of the ORs for skin and hub colonization.

The use of two different methods to diagnose CRI may have introduced some bias. Maki's technique, in fact, does not show the degree of colonization of the inner surface of the catheter and is less sensitive for diagnosing infections with the hub as portal of entry.[3] As a result, some CRIs associated with the hub could have been undetected in our study, leading to an underestimation of the OR for the hub. Another limit of the study is that cultures were not obtained of the infusate; however, given the low proportion of endemic infections due to contaminated infusate, this is not likely to have affected our results.[7]

Risk factor analysis by logistic regression confirmed the importance of skin colonization and hub colonization in causing catheter-related infections.

Both factors were associated with a consistent increase in the risk of infection; when all local and systemic infections were considered, skin colonization represented the greatest risk factor. Analysis of potential sources of infection suggested that the hub was more frequently responsible for severe infections, as confirmed by the risk factor analysis: when only symptomatic infections were considered, the risk associated with hub colonization was much higher than that associated with skin colonization. Several prospective studies have stressed the importance of the risk associated with skin colonization and the high prevalence of this risk factor among catheterized patients.[19,25-27]

By contrast, the risk of hub colonization, to date, has not been estimated by logistic regression analysis, and its association with more severe infections has not been clearly established. In the present study, skin and hub colonization was more often than not simultaneously present with colonization of the other site: skin-positive patients had a 26.5-fold risk of also having the hub positive, while hub-positive patients had a 15.9-fold increase in risk of simultaneous colonization of the skin.

Failure to adopt adequate patient-care practices (ie, handwashing, use of gloves, and aseptic techniques in manipulating the infusional set and the dressing) is likely to increase the risk of both skin and hub colonization. The duration of catheterization greatly influences the risk of infection,[18,19,28,29] leading some investigators to recommend scheduled replacement of catheters in order to reduce infection risk. However, the effectiveness of this approach has not been clearly established. A recent controlled trial[30] showed that routine replacement of CVCs every 3 days does not prevent infection and that replacement of catheters is associated with increased complications: mechanical complications when a new site is used and bloodstream infections when catheters are exchanged over a guidewire. Hence, the only effective preventive measure for reducing the risk associated with duration of exposure is to reduce unnecessary use of catheters. For peripheral catheters, Lederle[31] estimated that 35% of the 484 catheter episodes studied had two or more consecutive idle days. Comparable data is not available for central venous catheters.

Our study revealed two other risk factors for catheter infections: admission to surgical or coronary care units and a second episode of catheterization. Variability in the infection incidence observed in different hospital services probably is the effect of several factors, such as severity of patient mix, reason for catheterization, and the protocols used for patient care. A survey in 289 Italian ICUs in 1990 pointed out that 68% of the centers had a high level of compliance with recommended practices for catheter infection prevention,[32] whereas in other hospital services, standard protocols were adopted less frequently. The higher frequency of complications associated with the second episode of catheterization is probably due to the longer duration of stay in this group of patients and to more severe clinical conditions. Ena[33] estimated a 2.6-fold increase in the risk of catheter infections when the length of hospitalization was longer than 14 days. In order to define effective preventive strategies, it is necessary to identify which factors increase the risk of the two major determinants of catheter-related infections revealed in our analysis: skin and hub colonization.

The interpretation of our study's results for skin and hub regression models is limited partially by the fact that compliance with recommended catheter-care practices was not followed up and information on number of hub manipulations was not obtained

TABLE 7
INDEPENDENT RISK FACTORS FOR SKIN COLONIZATION

Risk Factor	Odds Ratio	CI_{95}
Hub colonization	25.2	7.39 to 86.2
Age (years)		
53 to 71, gauze dressing	5.70	1.41 to 23.1
>71, gauze dressing	13.4	3.13 to 57.0
53 to 71, transparent dressing	0.74	0.19 to 3.81
>71, transparent dressing	1.02	0.23 to 4.62
Duration of catheterization (days)		
Gauze dressing	0.73	0.35 to 1.52
Transparent dressing	5.39	2.93 to 9.89
Transparent dressing		
Age <53 / <7 days catheterization	1.78	0.23 to 14.0
Age 53 to 71 / <7 days catheterization	0.23	0.04 to 1.20
Age >71 / <7 days catheterization	0.14	0.02 to 0.81
Age <53 / ≥8 days catheterization	13.3	2.23 to 78.9
Age 53 to 71 / ≥8 days catheterization	1.71	0.64 to 4.56
Age >71 / ≥8 days catheterization	1.01	0.31 to 3.35
Jugular insertion		
Female	4.19	1.26 to 13.9
Male	29.3	11.2 to 76.7
Sex, male		
No jugular insertion	0.66	0.18 to 2.42
Jugular insertion	4.61	2.14 to 9.89

TABLE 8
RISK FACTORS FOR HUB COLONIZATION: UNIVARIATE ANALYSIS

Risk Factor	No. of Patients	Incidence /100	Unadjusted Odds Ratio	*P* Value
Duration of catheterization (days)				
≤7	211	1.4	1.0	
7 to 14	176	5.1	3.7	0.05
>14	80	10.0	7.7	0.003
Service				
CCU/ICU*	209	1.0	1.0	
Surgery	258	7.0	7.8	0.001
Jugular insertion				
No	254	2.4	1.0	
Yes	213	6.6	2.9	0.025
TPN				
No	208	1.0	1.0	
Yes	259	6.9	7.7	0.002
Place of insertion				
Ward	347	3.2	1.0	
Operating room	120	7.5	2.5	0.04
Skin colonization				
No	381	1.3	1.0	
Yes	86	17.4	15.9	0.00001

* Coronary care/cardiosurgical units, intensive care units

directly. In fact, an uneven distribution of the variables of interest across specific hospitals and a different level of compliance with the recommended practices for catheter care could confound the results of a multisite study. In order to exclude this possibility, an analysis of risk factors for skin colonization was carried out on a subgroup of 183 surgical patients studied in a single hospital. This subgroup was chosen because the distribution of the variables of interest allowed for an accurate comparison of risk factors (both jugular and other veins of access were used, and both gauze and transparent medication were used for catheter care). Male gender, jugular access, and hub colonization still were significant risk factors for skin colonization. ORs for age, transparent dressing, and duration of catheterization showed the same trend as those for the overall population but were not statistically significant (probably as a result of the reduced power of the smaller sample size).

The "reason for catheterization" represents a crude measure of the number of hub manipulations and does not yield an estimate of a dose-response relationship. However, it allowed us to adjust in the models for the effect of number of hub manipulations.

Four factors appeared to be responsible for skin colonization: age of the patient, jugular insertion, use of transparent polyurethane dressing, and duration of catheterization. In elderly patients, physiologic and anatomical changes of the skin have been described; the skin becomes thinner and drier, losing elasticity and fat.[34] This can contribute to an increased risk of skin colonization. Moreover, in elderly patients, an increased risk of gastrointestinal and meatal colonization has been detected during hospital stay.[35]

Other authors have suggested that internal jugular CVCs are more likely to become infected than subclavian catheters.[18,36] This can be attributed to the close proximity of the catheter insertion site to the oropharynx, to the higher temperature, and to the greater difficulty in maintaining the dressing in place; all three of these factors lead to heavier skin colonization, as pointed out by Maki.[37] It is interesting to note that the risk of skin colonization was higher among males, probably due to the presence of facial hair, which facilitates the multiplication of microorganisms. Moreover, shaving of patients with a barber brush, as still done in some Italian hospitals, can increase the risk of colonization of the skin with microorganisms carried on the brush or on the hands of the personnel.

The use of transparent dressings on CVC has become more common in the past 10 years, despite the fact that several small-sized randomized controlled trials have raised doubts as to its safety. Hoffmann[38] carried out a meta-analysis of seven studies of CVCs, concluding that there was a significant increase in the risk of catheter-tip infection when

using transparent dressings as opposed to gauze dressings (RR, 1.78, 1.38 to 2.30). The effect of the use of occlusive dressings on infection incidence is attributable to significant skin colonization. The results of our study are commensurate with these findings: in patients younger than 53 years with a duration of catheterization longer than 1 week, the risk of skin colonization increased by 13 times when a transparent dressing was used; the lack of a significant association in elderly patients is due to an increased risk of skin colonization in patients treated with gauze dressings (3.8% in subjects <53 years; 14.7% for 53 to 71 years; 22.3% for >71 years), as an effect of increasing age. Although our study showed an increase in the risk of skin colonization with transparent dressing, a number of questions still need to be answered, such as the relationship between the product used for skin disinfection and skin colonization under the dressing, or the impact of the interval between dressing changes and risk of skin colonization.[39] TPN constituted the major risk factor for hub colonization; this is probably attributable to more frequent manipulation of the catheter in patients for whom the catheter is used for administrating TPN.

Some of the risk factors reported by other authors were not confirmed by our study. For instance, triple-lumen catheters have been found to be associated with a higher risk of infection when compared with single lumens[40-42]; however, other trials have failed to demonstrate any significant difference in infection rates.[43-45] In our study, a very small proportion of multilumen catheters were used (5.8%), which can explain the lack of any association with catheter infections. The same applies to difficult insertion, which other investigators have identified as a relevant risk factor:[18,25] insertion was recorded to be difficult in only 4.5% of catheterizations performed.

Much progress has been made over the past 10 years in the prevention of catheter-related infections, but more efforts should be placed on developing measures that are capable of reducing skin and hub colonization, which are the two major determinants of endemic catheter infections. There are currently many interesting developments in the prevention of infections originating from the skin: use of more effective cutaneous antiseptics,[10] use of topical mupirocin,[46] and the development of promising new technologies such as a silver-impregnated cuff[47] and catheters coated with antimicrobials.[48] More work needs to be done to prevent hub colonization. Stotter had demostrated that a novel catheter hub more resistant to contamination was associated with a decreased rate of catheter-related septicemias.[49] Other authors also have designed contamination-resistant hubs, but their work has not been validated clinically.[50]

Our study shows that skin and hub colonization are the two major determinants for endemic CRIs. Skin colonization is the result of a complex causal model, where age, duration of catheterization, and type of dressing strongly interact. The highest risk of skin colonization associated with transparent dressing is in patients less than 53 years of age and with long duration of catheterization. The effect of duration of catheterization is no longer evident, while elderly patients show a significant increase in risk of skin colonization, when gauze dressing is used. Jugular access significantly increases the risk, particularly in males. Strategies for preventing skin colonization should be focused on specific subgroups of patients, defined in terms of demographic characteristics and type of care practices.

According to our study, hub colonization is less frequent but considerably increases the risk of systemic CRI. Therefore, prevention of hub colonization represents a top priority in order to reduce life-threatening infections. More efforts should be focused on understanding the causal model of hub colonization and developing effective control measures.

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