Jugular versus Femoral Short-Term Catheterization and Risk of Infection in Intensive Care Unit Patients

Causal Analysis of Two Randomized Trials

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***Rationale*: When subclavian access is not possible, controversy exists between the internal jugular and femoral sites for the choice of central-venous access in intensive care unit patients.**
***Objectives*: To compare infection and colonization rates of short-term jugular and femoral catheters.**
***Methods*: Using data from two multicenter studies, we compared femoral and internal jugular for the risks of catheter-related bloodstream infection, major catheter-related infection, and catheter-tip colonization. We also compared the rates of dressing disruption and skin colonization. We used marginal structural models with inverse probability of treatment weighting to adjust on indication bias.**
***Measurements and Main Results*: We included 2,128 patients (2,527 catheters and 19,481 catheter-days). We found no difference in catheter-related bloodstream infection (internal jugular 1.0 vs. femoral 1.1 per 1,000 catheter-days; hazard ratio [HR], 0.63 [0.25–1.63]; $P = 0.34$), major catheter-related infection (internal jugular 1.8 vs. femoral 1.4 per 1,000 catheter-days; HR, 0.91 [0.38–2.18]; $P = 0.34$), and colonization (internal jugular 11.6 vs. femoral 12.9 per 1,000 catheter-days; HR, 0.80 [0.25–1.63]; $P = 0.15$). However, colonization was higher with femoral for female (HR, 0.39 [0.24–0.63]; $P < 0.001$) and, at the significance limit, catheter maintained for more than 4 days (HR, 0.73 [0.53–1.01]; $P = 0.05$). The absence of benefit of internal jugular before Day 5 was related to a higher skin colonization at the internal jugular site for catheters removed before Day 5. After the fourth day, dressing disruption became more frequent with femoral catheters and may explain the subsequent risk of catheter colonization. Differences in cutaneous and catheter colonization between internal jugular and femoral was suppressed by the use of chlorhexidine-impregnated dressings.**

***Conclusions*: Femoral and internal jugular accesses lead to similar risks of catheter infection. Internal jugular might be preferred for female, nonchlorhexidine-impregnated dressings users, and when catheters are left in place more than 4 days. Both sites are acceptable when a subclavian approach is not feasible.**
Clinical trial registered with www.clinicaltrials.gov (NCT00417235 and NCT01189682).

Keywords: catheter-related infection; jugular; femoral catheter; prevention

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Controversies exist about the infectious risk of femoral venous catheters compared with internal jugular catheters. The respective indications for internal jugular and femoral routes are important, particularly if risk associated with barotrauma is high. Cohort studies and metaanalyses give conflicting results, probably because various confounders (particularly differences in case-mix) have been improperly taken into account and may interfere with conclusions.

What This Study Adds to the Field

In a secondary analysis of two large randomized controlled trials, where data were collected and checked in depth, and after careful adjustment on channeling bias using marginal structural models, we found that the risks of tip colonization and catheter-related bloodstream infection are similar between the femoral and internal jugular routes. However, the risk of catheter-tip colonization is higher with femoral catheters in women, when catheters were left in place more than 4 days, and when chlorhexidine-impregnated dressings are not used.

Catheter-related bloodstream infection (CR-BSI) is a frequent event in the intensive care unit (ICU) that could be substantially decreased by proper prevention strategies (1, 2).

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In ICU patients, extraluminal route of infection is predominant (3) and prevention should promote strategies that decrease cutaneous colonization at the catheter site. The proper choice of the catheter site may influence skin colonization and subsequent catheter colonization, and finally infection. The subclavian access has been repeatedly associated with a decrease in cutaneous colonization (4, 5), dressing disruptions (5, 6), catheter colonization, and infection rates (7–11) and is recommended in US and European guidelines (1, 12). However, it may be difficult to choose the subclavian route in patients with severe alteration of oxygenation and coagulation disorders, because of the increased risks of life-threatening barotraumas (13) and puncture of incompressible vessels (14). This explains why subclavian access is chosen in less than half of cases in ICU patients (15).

When the subclavian route is not indicated, controversy still exists about the advantage of internal jugular versus femoral access in preventing infection. Only one randomized controlled trial (RCT) conducted with hemodialysis ICU catheters concluded an absence of difference in catheter-tip colonization (16). Meta-analyses of cohort studies or of data recorded in RCTs on catheters (8, 9, 17) provided questionable results, because insertion site was not randomized and unmeasured confounding factors may persist.

To obtain unbiased estimates of the risk of femoral access as compared with internal jugular access, methods should account for obvious requirements: catheters need to remain in place long enough to become infected; and patients in whom physicians had inserted femoral or internal jugular catheters are different in term of usage of catheters and risk factors of catheter infection.

The purpose of this study was to carefully compare the risk of skin colonization, dressing disruption, catheter colonization, and CR-BSI, taking into account measurable confounding factors and duration of catheter insertion, and using marginal structural models. We used the data entered in two large RCTs (18, 19) in which extensive prospective high-quality data collection at catheter insertion and catheter removal was performed.

METHODS

Study Design

This study includes two longitudinal databases from two RCTs: Dressing (19) and Dressing2 (18). These studies had similar objectives: to determine the effect of the use of chlorhexidine gluconate (CHG) dressings (impregnated sponges or gel) on the colonization and infection of intravascular catheters in ICU. Studies were not masked to the investigators or ICU staff but were masked to the microbiologists processing the skin and catheter cultures and to the adjudication committee. Data were recorded by dedicated clinical research organization monitors in each center and extensively validated before data entry.

Study Patients

Dressing study took place from December 20, 2006 to May 20, 2008 in seven ICUs (from three university and two general hospitals) (19). Dressing2 study took place from May 31, 2010 to July 29, 2011 in 12 ICUs (from seven university and four general hospitals) (18). Characteristics of patients and catheters were similar between both studies. Body mass index (BMI) was only recorded in the Dressing2 study and in two ICUs in the Dressing study.

Study Catheters

This *post hoc* analysis used internal jugular venous catheter and femoral venous catheter inserted in both studies. The choice of the site of insertion was left to the discretion of the physician caring for the patient. All intravascular catheters in a given patient were managed identically. All study centers followed French recommendations for catheter insertion and care, which are similar to CDC recommendations (3). Maximal sterile barrier precautions (large sterile drape; surgical hand antisepsis; and mask, cap, sterile gloves, and gown) were used at catheter insertion. Dressings were changed 24 hours after catheter insertion (Day 1) and then every 3 or 7 days according to randomization scheme (Dressing) (19) or standard practice in each ICU (Dressing2) (18).

Patients underwent follow-up until 48 hours after ICU discharge. Catheters were immediately removed if no longer needed, or if a catheter-related infection (CRI) was suspected. Catheter tips were cultured using quantitative culture technique (20, 21). In both studies, skin colonization was assessed using semiquantitative insertion-site cultures; the insertion site was sampled as previously reported (18, 19) immediately before catheter removal by pressing a sterilized nutritive trypticase-soy agar plate containing antiseptic-neutralizing agents (Count-Tact, 3P Pack+; Biomerieux, Crapone, France) for 5–10 seconds on the skin, centering the plate on the insertion site. This agar plate contains CHG neutralizers that avoid *in vitro* artificial sterilization of cutaneous culture by inhibiting residual CHG effect. The plate was sent to the local microbiology laboratory and cultured for 48 hours. The number of CFU was counted. Because the size of the counting surface was different between both studies, we created a semiquantitative variable with sterile, +, ++, and +++ according to quartiles of quantitative cultures obtained in each study.

When a major-CRI (M-CRI) was suspected, one or more peripheral blood samples for culturing were collected within 48 hours before or after catheter removal. If the catheter-tip culture indicated colonization, or if a culture of blood sampled at catheter removal was positive, or when catheter culture was not performed, coordinating investigators (J.-F.T., J.-C.L.) helped by a clinical research senior monitor, all masked to the study group, reviewed the case-report form and medical chart to collect all the available information needed for an independent masked review. Then an independent adjudication committee masked to study groups classified these episodes according to the definitions described next.

Definitions

Three definitions were used, according to French and American guidelines (12, 22). First, catheter colonization was a positive quantitative catheter-tip culture. Second, catheter-related clinical sepsis without BSI was a combination of body temperature ($\geq$38.5°C or $\leq$36.5°C), catheter colonization, pus at the insertion site, or resolution of clinical sepsis after catheter removal, and absence of any other infectious focus. Third, CR-BSI was a combination of one or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal, a quantitative catheter-tip culture positive for the same microorganisms or a blood-culture differential time-to-positivity of 2 hours or more, and no other infectious focus explaining the positive blood cultures (8). In patients with blood cultures positive for coagulase-negative staphylococci, the same pulsotype in the catheter and blood cultures was required for a diagnosis of CR-BSI. M-CRI was either catheter-related clinical sepsis without bloodstream infection (category 2) or CR-BSI (category 3). For patients without catheter cultures, the adjudication committee determined whether M-CRI was present; sepsis or BSI were classified as catheter-related when there was no other detectable cause of sepsis with or without BSI. Noncultured catheters were classified as not colonized unless there was sepsis with no other detectable cause.

Statistical Analysis

Characteristics of patients and catheters were described as count (percent) or median (interquartile range) for qualitative and quantitative variables, respectively, and were compared between catheters groups using chi-square or Mann-Whitney tests, as appropriate.

Because the site of insertion was not randomized, we developed a propensity score (23) aimed to predict the probability that a given catheter would be inserted into the jugular vein, conditionally on variables recorded before and at the time of catheter insertion. The following clinically relevant variables were entered in the model: center; comorbidities, such as hematologic malignancy and chronic respiratory failure; main reason for ICU admission; mechanical ventilation with positive end-expiratory pressure greater than or equal to 6 cm H_2O within 24 hours after admission; admission for surgery (vs. medical); use of inotropes (dopamine $\geq$ 5 or epinephrine $\geq$ 0.1 or norepinephrine

≥ 0.1 μg/kg/min); bilirubin greater than 59 mg/L; platelet count less than 50,000/mm^3; creatinine greater than 34 mg/L; catheter inserted on the first day of ICU stay; antimicrobials at catheter insertion; and need for parenteral nutrition. Two-by-two interaction terms were also tested and added in the model when significantly associated with jugular insertion. Then, an inverse probability of treatment weighting (24) based on the propensity score was computed to create a pseudo-population in which the probability to receive a jugular and femoral catheter was equal, such as in a pure randomized design. Then, the effect of catheter insertion site on colonization, M-CRI, and CR-BSI was estimated using a Cox model for clustered data, weighted by inverse probability of treatment weighting. A hazard ratio (HR) less than one indicated a lower risk of event of internal jugular catheter compared with femoral catheter. This model takes into account intra-cluster (intrapatient) dependency (>1 catheter per patient), using robust sandwich covariance estimates (25) (PROC PHREG of SAS version 9.3; SAS Institute Inc., Cary, NC). Data were censored at 28 days since catheter insertion. The proportionality hazards assumption was tested with Schoenfeld residuals. Subgroup analyses were performed on the CHG and the non-CHG dressings subpopulation, using the first catheter only, according to the patient's sex (4, 11) and to the duration of catheter maintenance (<5 d and ≥5 d). Also, a propensity matched analysis was rerun to ensure the robustness of main results. Finally, another sensitivity analysis was computed in the 1,318 (1,552 catheters) patients (16), for whom BMI was available using the same methods. Details about statistical methods are in the online supplement.

We used multiple analysis of variance adjusted on the time of catheter in place to examine the number of dressing disruptions and the skin cultures at catheter removal between internal jugular and femoral accesses. Analyses were performed using SAS 9.3 (SAS Institute Inc.) and R (R Foundation for Statistical Computing, Vienna, Austria) software.

RESULTS

Patients and Catheters

A total of 2,128 patients with at least one internal jugular and/or one femoral catheter were included in the study, 1,022 (48%) from the Dressing study and 1,106 (52%) from the Dressing2 study (Figure 1). The data consisted of a total of 2,527 catheters and 19,481 catheter-days. Patient and catheter characteristics of the original population are reported in Tables 1 and 2.

The catheter colonization rate was 9.7% (246 events, 12.6 per 1,000 catheters-days), the M-CRI rate was 1.2% (31 events, 1.6 per 1,000 catheter-days), and the CR-BSI rate was 0.8% (20 events, 1 per 1,000 catheter-days).

There were 1,400 (55.4%) catheters placed in femoral site and 1,127 (44.6%) catheters placed in internal jugular site. In the femoral group, patients were more seriously ill and catheters were mainly inserted on the first day of ICU stay (60.9%), whereas catheters in the internal jugular group stayed longer than catheters in the femoral group (median [interquartile range], 7 [4–12] vs. 5 [3–8]).

Variables used to determine the risk for a catheter being inserted using the femoral route are in shown in Table E1 in the online supplement. The discrimination (area under the curve and receiver operating characteristic = 0.736) and calibration (Hosmer-Lemeshow chi-square P = 0.702) of the final model were acceptable.

Catheter Infection

There was no difference in CR-BSI or M-CRI between internal jugular and femoral catheters (Table 3). Results remained similar after adjustment for risk factors of CRI (*see* Table E3).

Catheter Colonization

The colonization rate was 12.9 per 1,000 catheter-days for femoral access and 11.6 per 1,000 catheter-days for internal jugular access (HR, 0.80; 95% confidence interval [CI], 0.59–1.08; P = 0.15) (Table 3 and Figure 2). Schoenfeld residuals analysis showed that impact of catheter site on colonization differed with time (P = 0.047). Whereas both sites provided similar colonization risk for the first 4 days of catheter maintenance (HR, 1.12; 95% CI, 0.55–2.28; P = 0.75), internal jugular access tend to reduce the risk of colonization after the fourth day (HR, 0.73; 95% CI, 0.53–1.01; P = 0.05) (Table 3). Results remained similar after adjustment on risk factors of catheter colonization (*see* Table E3).

Dressing Disruptions

The number of dressing disruptions per catheter-day was higher for femoral than for internal jugular catheters (0.20 vs. 0.18 dressing disruption per catheter-day; P = 0.05). The difference was significant for catheter maintained at least 5 days (P = 0.0007

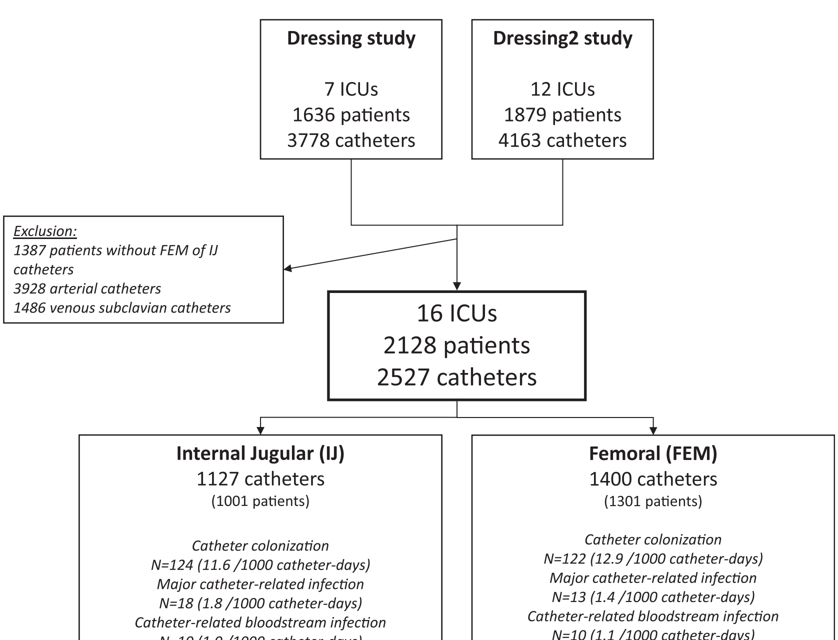


Figure 1. Flow chart. Two intensive care units (ICUs) were common in the two studies. Some patients had more than one catheter.

TABLE 1. PATIENTS' CHARACTERISTICS

Variable	All Patients (*n = 2,128*)	Patients with Jugular Catheter (*n = 1,001*)*	Patients with Femoral Catheter (*n = 1,301*)*	*P* Value
Age, median (IQR), yr	63 (51–74)	62 (51–73)	63 (51–74)	0.27
Men	1,387 (65.2)	664 (66.3)	837 (64.3)	0.32
⩾1 Comorbidities	733 (34.4)	351 (35.1)	444 (34.1)	0.64
Comorbidities				
Immune deficiency	124 (5.8)	51 (5.1)	82 (6.3)	0.22
Hematologic malignancy	70 (3.3)	29 (2.9)	47 (3.6)	0.34
Chronic respiratory failure	124 (5.8)	68 (6.8)	65 (5)	0.07
Metastatic cancer	114 (5.4)	48 (4.8)	76 (5.8)	0.27
AIDS	73 (3.4)	34 (3.4)	47 (3.6)	0.78
SAPS II, median (IQR)†	55 (42–70)	53 (42–67)	57 (43–71)	<0.01
SOFA, median (IQR)‡	11 (8–13)	10 (7–13)	11 (8–14)	0.04
Glasgow score <10	1,088 (51.1)	476 (47.6)	706 (54.3)	<0.01
Dopamine > 5 or epinephrine ⩾ 0.1 or norepinephrine ⩾ 0.1 μg/kg/min	1,318 (61.9)	574 (57.3)	849 (65.3)	<0.01
Bilirubin > 59 mg/L	123 (5.8)	58 (5.8)	77 (5.9)	0.90
Platelet < 50,000/mm^3	181 (8.5)	80 (8)	115 (8.8)	0.47
Creatinine > 34 mg/L	369 (17.3)	168 (16.8)	232 (17.8)	0.51
Admission category				<0.01
Medical	1,613 (75.8)	718 (71.7)	1,020 (78.4)	
Scheduled surgery	111 (5.2)	60 (6)	63 (4.8)	
Emergency surgery	404 (19)	223 (22.3)	218 (16.8)	
Main reason for ICU admission				<0.01
Septic shock	448 (21.1)	247 (24.7)	241 (18.5)	
Cardiogenic shock	208 (9.8)	72 (7.2)	150 (11.5)	
De novo respiratory failure	37 (1.7)	17 (1.7)	23 (1.8)	
Coma	230 (10.8)	83 (8.3)	164 (12.6)	
Trauma	139 (6.5)	51 (5.1)	107 (8.2)	
Mechanical ventilation	1,665 (78.2)	800 (79.9)	1,004 (77.2)	0.11
Mechanical ventilation PEEP ⩾ 6 cm H_2O	682 (32)	372 (37.2)	374 (28.7)	<0.01
Length of ICU stay, median (IQR), d	10 (5–22)	13 (6–28)	10 (4–21)	<0.01
ICU death	790 (37.1)	356 (35.6)	509 (39.1)	0.08
Hospital death	935 (43.9)	423 (42.3)	603 (46.3)	0.05

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; PEEP = positive end-expiratory pressure; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment.

Data are given as n (%) unless otherwise noted.

*A total of 173 patients had both femoral and jugular access and were counted in both groups.

† Range of possible scores, 0–162.

‡ Range of possible scores, 0–24.

for interaction term between number of dressing disruption and duration of catheter maintenance).

Skin Colonization at Catheter Removal

Skin colonization at catheter removal was significantly higher for internal jugular access than for femoral access in both non-CHG and CHG dressing groups ($P < 0.01$). The difference was significant for catheter maintained less than 5 days and became not statistically significant thereafter. This difference remained significant in males but was not significant in females (Table 4).

Subgroup and Confirmatory Analyses

The results remained very similar when using a propensity matched analyses, although the benefit for female of internal jugular was no longer significant (*see* Table E2) or when limiting the analyses to the first catheter inserted (*see* Table E5).

TABLE 2. CATHETER CHARACTERISTICS

Variable	All Catheters (*n = 2,527*)	Jugular Catheters (*n = 1,127*)	Femoral Catheters (*n = 1,400*)	*P* Value
Catheter on the first day	1,323 (52.4)	470 (41.7)	853 (60.9)	<0.01
Time in place, median (IQR), d	6 (4–10)	7 (4–12)	5 (3–8)	<0.01
Experience of the operator < 50 procedures	1,459 (57.7)	665 (59)	794 (56.7)	0.25
Use of lipids	997 (39.5)	472 (41.9)	525 (37.5)	0.03
Use of heparin	861 (34.1)	422 (37.4)	439 (31.4)	<0.01
Packed red blood cells transfused	874 (34.6)	400 (35.5)	474 (33.9)	0.39
Catheter removal for suspected infection	385 (15.2)	165 (14.6)	220 (15.7)	0.46
Dressing				0.14
Biopatch	644 (25.5)	312 (27.7)	332 (23.7)	
CHG	648 (25.6)	275 (24.4)	373 (26.6)	
HP	315 (12.5)	140 (12.4)	175 (12.5)	
Standard	920 (36.4)	400 (35.5)	520 (37.1)	
Antimicrobials at catheter insertion	1,547 (61.2)	761 (67.5)	786 (56.1)	<0.01

Definition of abbreviations: CHG = chlorhexidine gluconate; HP = high performance; IQR = interquartile range.

Data are given as n (%) unless otherwise noted.

TABLE 3. INCIDENCES AND HAZARD RATIOS OF JUGULAR AND FEMORAL CATHETERS

	Incidence, No. per 1,000 Catheter-Days		Unweighted		Weighted (*IPTW*)	
Variable	Jugular (*n* = *1,127*)	Femoral (*n* = *1,400*)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Catheter colonization > 1,000 CFUs per plate	11.6	12.9	0.74 (0.57–0.97)	0.03	0.80 (0.59–1.08)	0.15
Major catheter-related infection	1.8	1.4	0.90 (0.44–1.85)	0.77	0.91 (0.38–2.18)	0.84
Catheter-related bloodstream infection	1.0	1.1	0.67 (0.27–1.65)	0.39	0.63 (0.25–1.63)	0.34
Subgroup analysis according to the duration of catheter maintenance						
Catheters in place ≤4 d	n = 314	n = 616				
Catheter colonization > 1,000 CFUs per plate	22.7	16.3	1.37 (0.79–2.39)	0.27	1.64 (0.83–3.25)	0.15
Major catheter-related infection	0	0.6				
Catheter-related bloodstream infection	0	0.6				
Catheters in place >4 d	n = 813	n = 784				
Catheter colonization > 1,000 CFUs per plate	10.5	12.1	0.72 (0.54–0.97)	0.03	0.73 (0.53–1.01)	0.05
Major catheter-related infection	2.0	1.6	0.95 (0.45–2.01)	0.90	0.95 (0.39–2.30)	0.90
Catheter-related bloodstream infection	1.0	1.2	0.73 (0.29–1.85)	0.50	0.67 (0.25–1.78)	0.42
Subgroup analysis according to the use of CHG dressings						
Nonimpregnated dressings	n = 540	n = 695				
Catheter colonization > 1,000 CFUs per plate	15.2	21.0	0.59 (0.43–0.81)	0.001	0.66 (0.45–0.95)	0.03
Major catheter-related infection	2.7	2.2	0.87 (0.38–2.00)	0.75	0.96 (0.35–2.66)	0.94
Catheter-related bloodstream infection	1.2	2.0	0.49 (0.17–1.41)	0.18	0.50 (0.17–1.52)	0.22
Impregnated dressings	n = 587	n = 705				
Catheter colonization > 1,000 CFUs per plate	8.4	5.2	1.40 (0.84–2.34)	0.19	1.46 (0.85–2.51)	0.17
Major catheter-related infection	1.0	0.6	1.04 (0.24–4.43)	0.96	0.75 (0.17–3.38)	0.71
Catheter-related bloodstream infection	0.8	0.2	2.42 (0.25–23.24)	0.44	1.99 (0.22–18.44)	0.54
Subgroup analysis according to the sex						
Male (n = 1,645)	n = 739	n = 906				
Catheter colonization > 1,000 CFUs per plate	12.9	10.9	1.02 (0.73–1.43)	0.90	1.13 (0.77–1.65)	0.54
Major catheter-related infection	1.5	1.3	0.91 (0.36–2.33)	0.85	0.95 (0.30–2.96)	0.92
Catheter-related bloodstream infection	0.8	1.1	0.53 (0.17–1.66)	0.28	0.41 (0.13–1.33)	0.14
Female (n = 882)	n = 388	n = 494				
Catheter colonization > 1,000 CFUs per plate	9.2	17.0	0.40 (0.26–0.63)	<0.01	0.39 (0.24–0.63)	<0.01
Major catheter-related infection	2.3	1.6	0.90 (0.28–2.85)	0.85	0.94 (0.27–3.31)	0.92
Catheter-related bloodstream infection	1.4	1.0	0.96 (0.20–4.55)	0.96	1.38 (0.27–6.95)	0.70

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting.
HR < 1 is in favor of a lower risk for internal jugular catheters.

In catheters dressed with nonimpregnated dressings, internal jugular access led to a significant decrease in the risk of colonization (15.2 vs. 21.0 per 1,000 catheter-days; weighted HR, 0.66; 95% CI, 0.45–0.95; P = 0.03) with no impact of CR-BSI and M-CRI. In the case of catheters dressed with impregnated dressings, there was no difference for catheter colonization or infection.

The benefit of internal jugular access on colonization was significant for female only and for catheter maintained for more than for 4 days.

Finally, the result of the same model on the subgroup for whom the BMI was available did not find difference between internal jugular and femoral in the lowest and upper classes of BMI (*see* Tables E6 and E7).

DISCUSSION

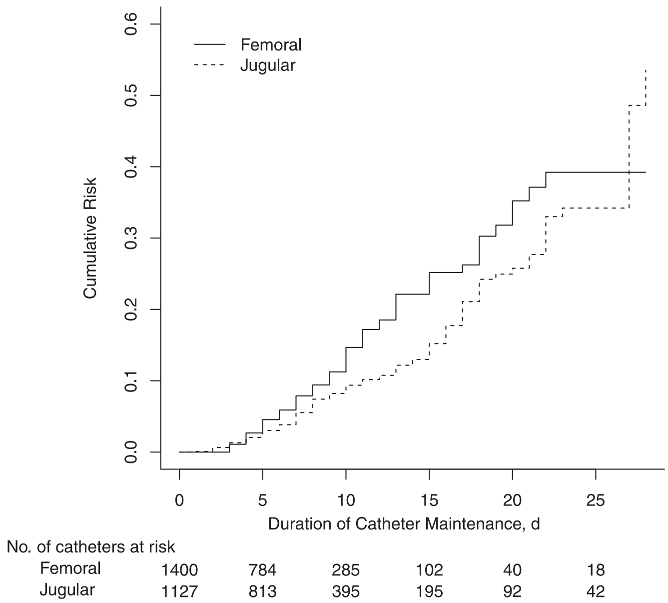
We have shown in an environment of consistent central venous catheter care during large multicenter RCTs, careful data monitoring and data entry, and use of causal analysis for careful adjustment on indication (or channeling) bias, that the rate of M-CRI, CR-BSI, and colonization was not different between internal jugular and femoral accesses.

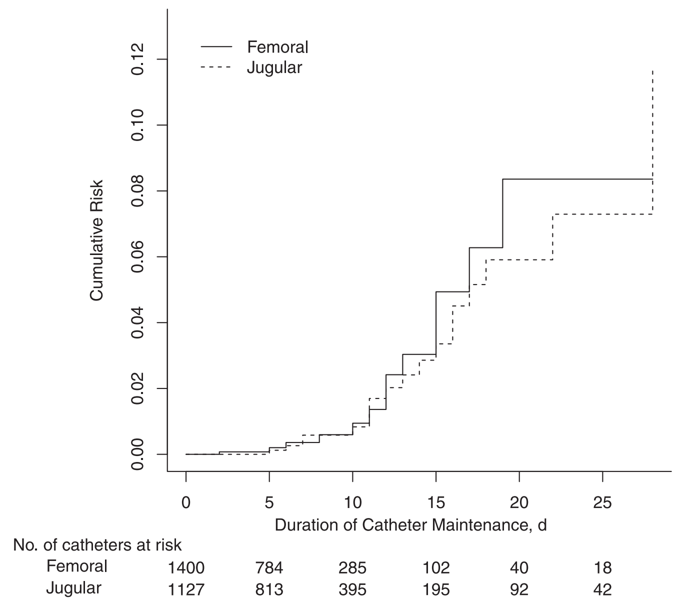
Subgroup analyses found that internal jugular access decreased the risk of colonization of the catheter tip for female, non-CHG impregnated dressings, and catheters maintained at least 5 days, but failed to find differences in CR-BSI or M-CRI rates. Dressing disruption occurred more frequently for femoral catheters, mainly for catheter maintained less than 5 days. Finally, cutaneous colonization at central venous catheter removal occurred more frequently for internal jugular catheters, especially in males and when catheters are maintained less than 5 days.

The risk for catheter infections is related in part to the density of local skin flora (4–6). Femoral and internal jugular sites both carry obvious sources of contamination from groin and oral secretions. The skin colonization may also depend on patients' characteristics. It increases in case of dressing disruption (5) and of high pilocebaceous unit density (4, 11).

The skin may have experienced microscopic cuts and abrasions during the process of shaving immediately before catheter insertion (26). Shaving may have promoted microorganism contamination of the skin around the catheter insertion and catheter colonization. The increased density of pilocebaceous unit in the neck in males may explain the sex difference. The increased risk of internal jugular skin contamination and catheter colonization during the first 4 days is prevented by CHG-impregnated dressings, confirming previous *in vitro* studies (27).

Skin colonization and dressing disruption are key factors explaining catheter colonization and infection in ICUs (4–6). Cutaneous colonization at catheter removal was higher in the internal jugular group for catheters maintained less than 5 days, and in males. Conversely, the number of dressing disruption per catheter-day was slightly, but significantly, higher in the femoral group, especially after 4 days of catheter maintenance. These findings may be explained by the dermabrasion and pilocebaceous gland irritation that occurred during preparation of the insertion site. It may explain why the risk of catheter colonization tended to be lower when internal jugular access was used in females, and lower when catheters were inserted for at least 5 days.





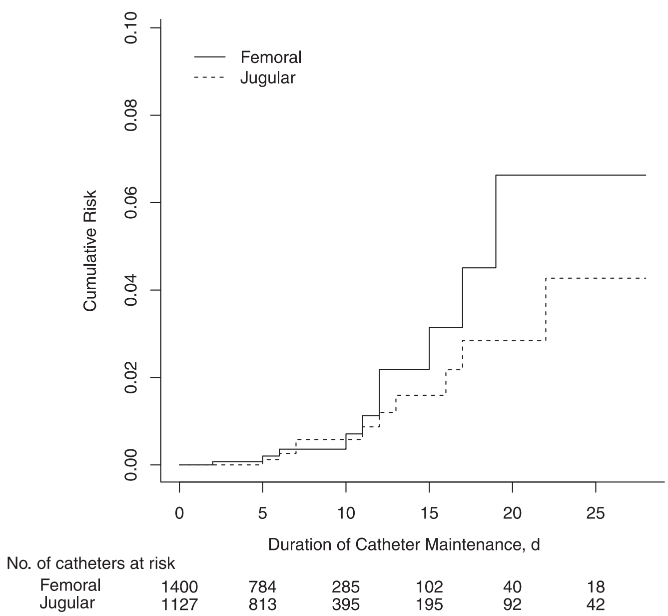


Figure 2. Cumulative incidence curve of colonization (*top left*), major catheter-related infection (M-CRI) (*top right*), and catheter-related bloodstream infection (CR-BSI) (*bottom*). The cumulative risk estimations used the Kaplan-Meier estimator under the hypothesis of non-informative censoring.

Our results that internal jugular and femoral catheter placement display a similar infectious risk are in line with recent published studies (8, 9, 11), but contradict the result of a recent cohort study performed by Lorente and coworkers (28). They found a twofold increase in the risk of CR-BSI associated with femoral access (9.52 vs. 4.83 per 1,000 catheter-days; risk ratio, 1.93; 95% CI, 1.03–3.73; $P = 0.04$). However, in this study, some of the catheters were inserted in the emergency room, and the CR-BSI rate was considerably higher than those obtained using strict aseptic conditions in an ICU setting.

The computation of the propensity score confirmed that in clinical practice, the femoral route is more likely to be selected than the jugular route in the most severe patients. Compared with the internal jugular site, the unadjusted risk of catheter colonization was significantly higher in the femoral site, in accordance with the result of Marik and coworkers (8). However, this association disappeared after controlling for the propensity to select one site, emphasizing the magnitude of the channeling bias for this comparison.

In the sentinel study from Parienti and coworkers (16), where the comparison referred to hemodialysis catheter inserted in ICU and one fifth of the catheters were antiseptic impregnated making the catheter more prone to be manipulated, the rate of catheter colonization was considerably higher than in the present study. Risk factors found with catheters used to administer drugs may not be applied to hemodialysis catheters used in ICU. Nevertheless, the weighted HR we found (0.80; 95% CI, 0.59–1.08; $P = 0.15$) is very consistent with the HR of 0.85 (95% CI, 0.59–1.16; $P = 0.31$) found by Parienti and coworkers (16).

We made particular effort to adjust on all the confounders that have been prospectively collected by trained investigators and study monitors during both RCTs. However, unmeasured factors may remain and cause residual confounding. In particular, we did not have individual information on the percentage of tracheostomized patients and on the rate of diarrhea episodes.

Indeed, tracheostomy has been shown to influence the risk of catheter infection for the internal jugular site (29) and diarrhea episode may favor skin colonization (30) around the

TABLE 4. SKIN CULTURE AT CATHETER REMOVAL FOR JUGULAR AND FEMORAL CATHETERS (MAIN AND SUBGROUP ANALYSES)

Skin Culture	Jugular (*n* = *755*)	Femoral (*n* = *1,042*)	*P* Value*
Sterile	282 (37.4)	487 (46.7)	0.0092
+	151 (20)	205 (19.7)	
++	180 (23.8)	188 (18)	
+++	142 (18.8)	162 (15.6)	
Men only	n = 512	n = 673	
Sterile	179 (35)	301 (44.7)	0.011
+	107 (20.9)	135 (20.1)	
++	123 (24)	130 (19.3)	
+++	103 (20.1)	107 (15.9)	
Women only	n = 243	n = 369	
Sterile	103 (42.4)	186 (50.4)	0.52
+	44 (18.1)	70 (19)	
++	57 (23.5)	58 (15.7)	
+++	39 (16.1)	55 (14.9)	
Catheters in Place <5 d	n = 188	n = 438	
Sterile	82 (43.6)	238 (54.3)	0.006
+	37 (19.7)	97 (22.2)	
++	45 (23.9)	61 (13.9)	
+++	24 (12.8)	42 (9.6)	
Catheter in Place ⩾5 d	n = 567	n = 604	
Sterile	200 (35.3)	249 (41.2)	0.20
+	114 (20.1)	108 (17.9)	
++	135 (23.8)	127 (21)	
+++	118 (20.8)	120 (19.9)	
Non-CHG dressings	n = 346	n = 502	
Sterile	119 (34.4)	213 (42.4)	0.51
+	64 (18.3)	81 (16.1)	
++	81 (23.4)	100 (20)	
+++	82 (23.3)	108 (21.5)	
CHG dressings	n = 409	n = 540	
Sterile	163 (39.9)	274 (50.7)	0.0016
+	87 (21.3)	124 (23)	
++	99 (24.2)	88 (16.3)	
+++	60 (13.7)	54 (10)	

Definition of abbreviation: CHG = chlorhexidine gluconate.
Skin culture was performed for 1,797 catheters. Data are given as n (%).
* *P* values are adjusted on the day of catheter maintenance at catheter removal.

femoral site. Although the presence of a tracheostomy was not prospectively collected during the study period, the overall rate of tracheostomized patients during the study period in the participating ICUs was less than 2%. Moreover, the rate of patients who received parenteral nutrition was taken into account in the analysis.

Also, the higher risk of deep venous thrombosis with femoral catheters (30–33), which is also high for internal jugular catheters (34), balanced with the risk of barotraumas with internal jugular access, should also be taken into account to make the decision at the bedside.

Finally, the rate of CRI was low, and our study may be underpowered to conclude equivalence between femoral and internal jugular accesses. However, the comparability of rates of colonization observed between internal jugular and femoral accesses, especially before the fifth day of catheter maintenance, appeared sufficient.

We conclude that, when properly adjusted to the propensity to insert at a specific site, femoral and internal jugular access were associated with a similar risk of infection and colonization. Because of the higher rate of catheter colonization with femoral catheters, internal jugular access may be preferred in women. The risk of catheter colonization is comparable between jugular and femoral routes when catheters are left in place less than 5 days. The risk of catheter colonization becomes higher for femoral access after this date and argues for removing femoral catheters on the fifth day if central venous access is subsequently needed.

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