Randomized Controlled Trial of Chlorhexidine Dressing and Highly Adhesive Dressing for Preventing Catheter-related Infections in Critically Ill Adults

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Rationale: **Most vascular catheter-related infections (CRIs) occur extraluminally in patients in the intensive care unit (ICU). Chlorhexidine-impregnated and strongly adherent dressings may decrease catheter colonization and CRI rates.**

Objectives: **To determine if chlorhexidine-impregnated and strongly adherent dressings decrease catheter colonization and CRI rates.**

Methods: **In a 2:1:1 assessor-masked randomized trial in patients with vascular catheters inserted for an expected duration of 48 hours or more in 12 French ICUs, we compared chlorhexidine dressings, highly adhesive dressings, and standard dressings from May 2010 to July 2011. Coprimary endpoints were major CRI with or without catheter-related bloodstream infection (CR-BSI) with chlorhexidine versus nonchlorhexidine dressings and catheter colonization rate with highly adhesive nonchlorhexidine versus standard nonchlorhexidine dressings. Catheter-colonization, CR-BSIs, and skin reactions were secondary endpoints.**

Measurements and Main Results: **A total of 1,879 patients (4,163 catheters and 34,339 catheter-days) were evaluated. With chlorhexidine dressings, the major-CRI rate was 67% lower (0.7 per 1,000 vs. 2.1 per 1,000 catheter-days; hazard ratio [HR], 0.328; 95% confidence interval [CI], 0.174–0.619; $P = 0.0006$) and the CR-BSI rate 60% lower (0.5 per 1,000 vs. 1.3 per 1,000 catheter-days; HR, 0.402; 95% CI, 0.186–0.868; $P = 0.02$) than with nonchlorhexidine dressings; decreases were noted in catheter colonization and skin colonization rates at catheter removal. The contact dermatitis rate was 1.1% with and 0.29% without chlorhexidine. Highly adhesive dressings decreased the detachment rate to 64.3% versus 71.9% ($P < 0.0001$) and the number of dressings per catheter to two (one to four) versus three (one to five) ($P < 0.0001$) but increased skin colonization ($P < 0.0001$) and catheter colonization (HR, 1.650; 95% CI, 1.21–2.26; $P = 0.0016$) without influencing CRI or CR-BSI rates.**

Conclusions: **A large randomized trial demonstrated that chlorhexidine-gel–impregnated dressings decreased the CRI rate in patients in the ICU with intravascular catheters. Highly adhesive dressings decreased dressing detachment but increased skin and catheter colonization.**

Clinical trial registered with www.clinicaltrials.gov (NCT 01189682).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Chlorhexidine-impregnated sponges decrease catheter-related infections (CRI) in the intensive care unit (ICU) but make impossible the continuous inspection of insertion site. Dressing disruption is frequent in the ICU and a major risk factor of CRI.

What This Study Adds to the Field

Chlorhexidine-impregnated gel dressings decrease by 60% the risk of CRI in the ICU. This second large, multicenter randomized control trial confirmed the benefits of chlorhexidine dressings. A highly adhesive nonchlorhexidine transparent dressing decreased dressing disruption but increased cutaneous and positive catheter tip culture.

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Central venous catheter (CVC)–related bloodstream infections (BSIs) are associated with attributable mortality rates of up to

11.5% and excess intensive care unit (ICU) stay lengths of up to 12 days (1, 2). The universally accepted method for minimizing catheter-related (CR) BSIs is a bundle of care combining maximal sterile barrier precautions for insertion, an appropriate antiseptic solution for skin antisepsis and line access, preferential subclavian catheterization, and immediate removal of unnecessary catheters (3, 4). Combining this catheter-care bundle with continuous quality improvement programs can decrease the CR-BSI rate below 2 per 1,000 CVC days (5, 6). In Europe, the incidence of CR-BSIs ranges from 1 to 3.1 per 1,000 patient-days (7) and in the French surveillance network fewer than 1 CR-BSI occurred per 1,000 CVC-days in 2010 (8). However, rates below 2 per 1,000 CVC-days are difficult to achieve in all ICUs (9) and in the long term (10).

Most organisms responsible for short-term CR-BSIs originate from the insertion site (11). Dressings often become detached in patients in the ICU (12). Decreasing bacterial skin colonization at the insertion site by improving dressing adhesion or using antiseptic-impregnated dressings may decrease the CR-BSI risk. We recently demonstrated that a chlorhexidine-impregnated sponge (BioPatch; Ethicon, Inc., Somerville, NJ) placed over the CVC insertion site under a standard dressing decreased major catheter infections (major-CRIs) by 60% and CR-BSIs by 76% (13). However, the sponge concealed the insertion site. In the same study, dressing replacement because of soiling or detachment was 67% (13). The new transparent chlorhexidine-impregnated gel dressing (Tegaderm CHG [chlorhexidine gluconate] IV Securement Dressing; 3M, St. Paul, MN) with high holding power and reinforced border has not previously been compared with standard dressings or nonimpregnated highly adhesive dressings.

The aim of this study in adult patients in the ICU was to evaluate the ability of Tegaderm CHG to decrease the rate of major-CRIs (CR sepsis with or without CR-BSI) and the ability of a highly adhesive nonantiseptic dressing to decrease dressing loosening and subsequent catheter colonization.

METHODS

Ethics Statement

The study was approved by the Rhône-Alpes-4 ethics committee, France. Informed consent was obtained from patients or surrogates.

Study Design

We used a multicenter randomized design to compare three types of transparent dressings: (*1*) a CHG dressing (Tegaderm CHG); (*2*) a highly adhesive dressing (Tegaderm HP Transparent Film Dressing, 3M); and (*3*) a standard breathable, hypoallergenic dressing (Tegaderm Transparent Film Dressing, 3M). The study was not masked to the investigators or ICU staff but was masked to the microbiologists processing the skin and catheter cultures and to the adjudication committee.

Study Patients

From May 31, 2010, to July 29, 2011, we recruited adults (>18 yr) admitted to 12 ICUs in seven university and four general hospitals and expected to require intravascular catheterization for 48 hours. Patients with known allergies to chlorhexidine or transparent dressings were excluded.

Patients were randomly assigned to one of three dressings, all used as part of standard care. Randomization was by a web-based random-number generator producing permuted blocks of eight, with stratification on ICUs. Each block contained four allocations to the chlorhexidine dressing, two to the highly adhesive dressing, and two to the standard dressing. The investigators were unaware of the block size and of the permutation procedure.

Study Catheters

All intravascular catheters in a given patient were managed according to the randomized dressing assignment. Pulmonary arterial, hemodialysis, peripherally inserted venous catheters, and catheters inserted before ICU admission were not included.

All study centers followed French recommendations for catheter insertion and care, which are similar to Centers for Disease Control and Prevention recommendations (14). The insertion sites were the radial artery and subclavian vein, unless using these sites carried an increased risk of noninfectious complications (15). Maximal sterile barrier precautions (large sterile drape; surgical hand antisepsis; and wearing a mask, cap, gown, and sterile gloves) were used at catheter insertion. Antiseptic skin preparation was with alcoholic povidone-iodine (PVI) or alcoholic chlorhexidine solution in accordance to standard procedure in each ICU. First, the insertion site was scrubbed with a detergent (4% aqueous PVI solution, Betadine Scrub; Viatris Pharmaceuticals, Merignac, France) or 4% chlorhexidine solution (Hibiscrub; Molnlycke Health Care, Wasquehal, France); rinsed with sterile water; and dried with sterile gauze. An alcohol-based antiseptic solution (5% PVI in 70% ethanol [Betadine Alcoholic Solution; Viatris Pharmaceuticals] or 0.5% chlorhexidine, 67% ethanol [Molnlycke Health Care]; or 0.25% chlorhexidine, 0.025% benzalkonium chloride, 4% benzyl alcohol [Biseptine Bayer Healthcare, Gaillard, France]) was then applied for at least 1 minute, and sterile drapes were placed around the site. Antiseptic- or antibiotic-impregnated catheters were not used in any of the study ICUs. Dressings were changed 24 hours after catheter insertion (Day 1) then every 3 or 7 days according to standard practice in each ICU. Leaking or soiled dressings were changed immediately. Alcoholic PVI solution or alcoholic chlorhexidine was used for skin antisepsis during dressing changes.

Suspected contact dermatitis or skin allergy was confirmed by a dermatologist. The investigator could decide to stop using the allocated dressing in patients with suspected skin reactions. The independent data safety committee was alerted immediately, as was the French Drug Agency and 3M.

Patients were followed until 48 hours after ICU discharge. Catheters were immediately removed if no longer needed (usually before ICU discharge) or if a CRI was suspected. Catheter tips were cultured using a simplified quantitative broth dilution technique with vortexing in 11 ICUs and sonication in one ICU (16, 17). In patients who needed to keep the CVC beyond ICU discharge, paired blood samples were drawn simultaneously from the catheter hub and a peripheral vein before ICU discharge for determination of the differential time-to-positivity (18).

Skin colonization was assessed using semiquantitative insertion-site cultures; the insertion site was sampled as previously reported (13) before catheter removal by pressing a sterilized nutritive trypticase-soy agar plate containing antiseptic-neutralizing agents (Count-Tact, 3P Pack+; Biomerieux, Crapone, France) for 10 seconds on the skin, centering the plate on the insertion site. This agar plate contains chlorhexidine neutralizers that avoid *in vitro* artificial sterilization of cutaneous culture by inhibiting residual chlorhexidine effect. The plate was sent to the local microbiology laboratory and cultured for 48 hours. The number of colony-forming units (CFU) was counted.

When major-CRI was suspected, one or more peripheral blood samples for culturing were collected. 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, an external investigator (J.-F.T.) helped by a clinical research senior monitor, masked to the study group, reviewed the case-report form and medical chart to collect all the available information needed to prepare an independent masked review.

Then, an independent adjudication committee (J.-R.Z., C.S., and C.A.) masked to study group classified all these episodes according to the definitions discussed next.

Definitions and Primary Evaluation Criteria

According to French (14) and American (19) guidelines, catheter colonization was a positive quantitative catheter-tip culture ($\geq$1,000 [17] or $\geq$100 [16] CFU/ml). When the catheter was not removed, the catheter was considered colonized in case of a positive blood culture from the catheter hub. CR clinical sepsis without BSI was a combination (a+b+c+d) of (*a*) body temperature greater than or equal to 38.5°C or less than or equal to 36.5°C; (*b*) catheter colonization; (*c*) pus at the

insertion site or resolution of clinical sepsis after catheter removal (resolution of fever or hypothermia within 24 h before any change of antimicrobial therapy); and (*d*) absence of any other infectious focus. CR-BSI was a combination of (*a*) one or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal; (*b*) a positive quantitative catheter-tip culture positive (using the 1,000 CFU/ml threshold when vortexing technique was used [17] or 100 CFU/ml threshold when sonication technique was used [16]) for the same microorganisms (same species and same susceptibility pattern) or a blood-culture differential time-to-positivity of 2 hours or more; and (*c*) no other infectious focus explaining the positive blood cultures (18). In patients with blood cultures positive for coagulase-negative staphylococci, the same pulse-field gel electrophoresis patterns (20) in the catheter tip and blood cultures was required for a diagnosis of CR-BSI. Major-CRI was either CR clinical sepsis without BSI or CR-BSI. For patients without catheter cultures, the blind adjudication committee determined whether major-CRI was present, with sepsis or BSI being classified as CR 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.

The primary endpoint was the catheter colonization rate for highly adhesive nonchlorhexidine dressings versus standard (nonchlorhexidine) dressings and the major-CRI rate for chlorhexidine dressings versus nonchlorhexidine dressings.

Secondary Evaluation Criteria

Secondary evaluation criteria were the rates of dressing changes because of detachment, CR-BSI, and skin colonization. The condition of the skin was described on a standardized form by the nurse in charge of the patient at each dressing change and at catheter removal, using the International Contact Dermatitis Research Group system (21). Finally, according to suggestion from external experts, for purpose of comparison with other studies, in a *post hoc* secondary masked analysis, episodes were reclassified as central line–associated BSI (CLA-BSI) according to Centers for Disease Control and Prevention definitions (22).

Number of Patients and Catheters

Our main working hypothesis was that the chlorhexidine dressing would decrease the 3% CRI rate with the standard dressing by 61% (13). Based on data from the study ICUs and a previous study (13), we expected at least two catheters per patient and an intraclass correlation of 0.02 (23). We used $\alpha = 5\%$ and $1\text{-}\beta = 80\%$ to compute sample size. We planned to enroll 1,888 patients (>3,776 catheters).

Statistical Analysis

Analyses were performed in the intent-to-treat population, which included all patients except those who withdrew their consent to study participation. No interim analysis was planned. All the analyses were planned ahead of the database lock, except the comparison of CLA-BSI rates, and subgroups analysis differentiating arterial catheters and CVCs.

Characteristics of patients, catheters, and dressings are described as n (percent) or median (interquartile range [IQR]) for categorical and continuous variables, respectively, and were compared among treatment groups using chi-square or Mann-Whitney tests, as appropriate. Kaplan-Meier curves of the risks of major-CRI and catheter colonization were plotted for each treatment group.

To take into account a possible clustering effect of multiple catheters per patient (with the cluster being the patient), we used a marginal Cox model for clustered data. This model takes into account the censored nature of the data and accounts for intracluster (intrapatient) dependence (more than one catheter per patient) using a robust sandwich covariance estimate (24) (PROC PHREG of SAS Software, version 9.3; SAS Institute, Inc. Cary, NC). Analyses were stratified by ICU. We checked the proportional hazards assumption and looked for qualitative interactions between treatment effects and among treatment centers (25). Heterogeneity of treatment effects was checked among various predefined patient subgroups.

For skin culture comparisons, clustering of the data was not taken into account. Skin cultures were classified into four groups: (*1*) sterile, (*2*) CFU less than 1 $\log_{10}$, (*3*) CFU = 1–2 $\log_{10}$, and (*4*) CFU greater than or equal to 2 $\log_{10}$. A Cochran-Armitage test for trend was used to compare skin colonization according to the evaluation criterion studied. The CFU skin counts with and without chlorhexidine dressings were compared using a Mann-Whitney test.

The secondary analyses were not controlled for multiple testing. Analyses were performed using SAS (version 9.3; SAS Institute, Inc.) and R (R foundation; Vienna, Austria). *P* values less than or equal to 5% were considered significant.

RESULTS

Patients and Catheters

Of 2,054 patients with at least one catheter, 1,898 could be enrolled and 1,879 were assessable for the intent-to-treat analysis (Figure 1), for a total of 4,163 catheters and 34,339 catheter-days. Patient and catheter characteristics are reported in Tables 1 and 2.

A total of 651 catheter files were blindly reviewed, 354 of which were easily classified by adjudicators. The remaining 297 files needed further details from investigators. Of these files, 239 were easily classified by one adjudicator, and 58 were considered debatable by the first adjudicator and submitted to the expert panel. Advice was unanimous for 31, and solved by discussion in the 27 remaining ones (CR-BSI in 8 cases, catheter sepsis without BSI in 8 cases, no infection in the 11 remaining cases).

The final diagnoses obtained at the database lock were as follows: catheters were colonized in 260 cases, CR-BSI in 31 cases, and CR clinical sepsis without BSI in 20 cases (pus at the insertion site was present in only one case).

In the nonchlorhexidine groups, overall numbers of colonized catheters, major-CRIs, and CR-BSIs were 186, 36, and 22, respectively, yielding incidence rates of 10.9, 2.1, and 1.3 per 1,000 catheter-days, respectively.

Overall Data on Dressing Changes

At the 14,019 dressing changes, 4,305 (30.7%) dressings were intact; 4,185 (29.9%) were detached; 3,781 (27%) were soiled; and 1,748 (12.5%) were detached and soiled. For the 2,201 arterial catheters, 72.8% of dressing changes occurred earlier than scheduled. For the 1,962 CVCs, early dressing changes were more common at the jugular and femoral veins (3,227 [71.3%] of 4,523) than at the subclavian vein (946 [50.1%] of 1,888; $P < 0.0001$; Mann-Whitney test).

Chlorhexidine versus Nonchlorhexidine Dressings

With chlorhexidine, the major-CRI rate decreased from 2.11 per 1,000 to 0.69 per 1,000 catheter-days (hazard ratio [HR], 0.328; 95% confidence interval [CI], 0.174–0.619; $P = 0.0006$) (Figure 2). The chlorhexidine group had significantly fewer CR-BSIs and colonized catheters (Table 3) (*see* Figure E1 in the online supplement), with similar effects on gram-negative and gram-positive organisms (*see* Table E1). The effects were not significantly influenced by type of antiseptic (alcoholic-PVI or alcoholic-chlorhexidine); scheduled dressing-change interval (3 or 7 d); admission category (surgical vs. medical); baseline Simplified Acute Physiology Score II score; or insertion site (*see* Figure E2).

Chlorhexidine dressings were estimated to prevent one major-CRI for every 71 catheters (95% CI, 57–125 catheters) left for a mean of 10 days. Similarly, CLA-BSI rate significantly decreased between groups 2.3 versus 0.9 per 1,000 catheter-days (HR, 0.367; 95% CI, 0.205–0.656; $P < 0.001$).

Highly Adhesive Nonchlorhexidine Dressings versus Standard Dressings

Overall data on dressing changes are given in the online supplement. Early dressing changes were significantly less common in the highly adhesive group (64.3%) than in the standard group (71.9%) ($P < 0.001$). The median (IQR) number of dressing

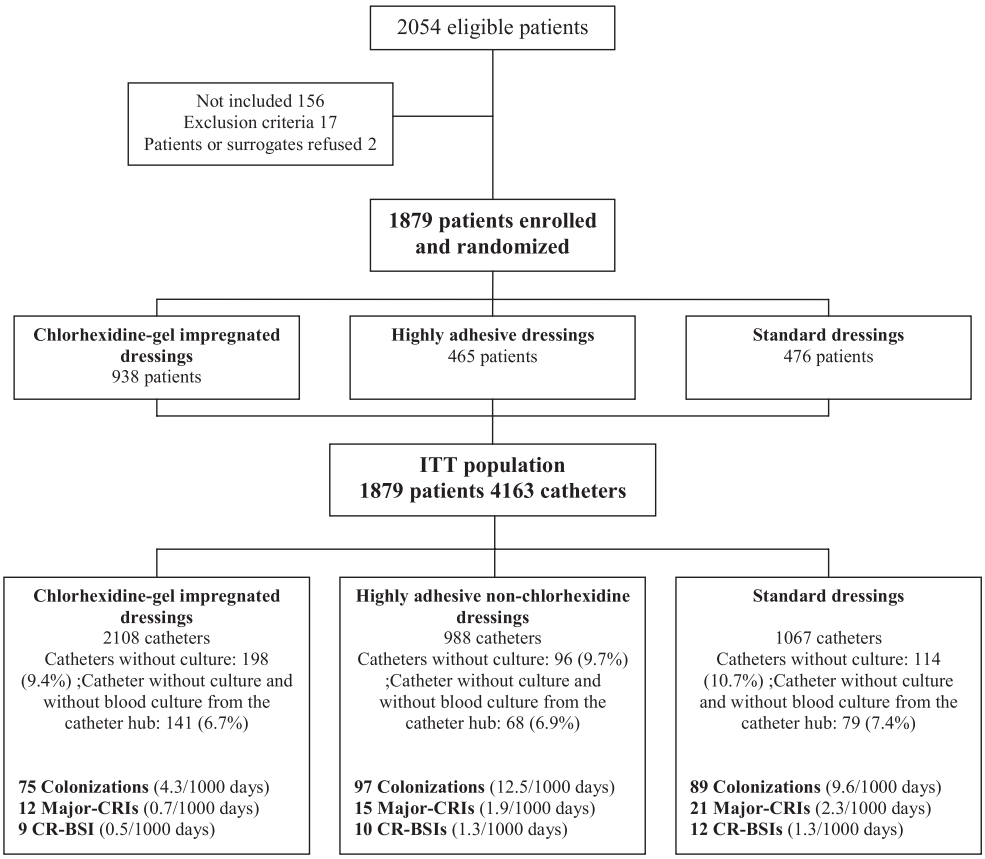

Figure 1. Flow chart of the study. CR-BSI = catheter-related bloodstream infection; CRI = catheter-related infections; ITT = intention to treat.

changes per catheter-days was significantly lower in the highly adhesive group (0.33 [0.20–0.50] per catheter-day; $P < 0.0001$; Mann-Whitney test) than in the standard group (0.36 [0.25–0.56] per catheter-day). The catheter colonization rate was significantly higher in the highly adhesive group compared with the standard group (Table 3 and Figure 2) (HR, 1.651; 95% CI, 1.208–2.256; $P = 0.0016$). The major-CRI and CR-BSI rates were not significantly different between these two groups (Table 3; *see* Figure E1). Also, CLA-BSI rate was not different between groups (HR, 1.284; 95% CI, 0.674–2.446; $P = 0.45$).

The incidence of colonization, major-CRI, and CR-BSI was not different between arterial catheters and CVCs. There was no heterogeneity of the chlorhexidine-impregnated effect and catheter types (*see* Table E2).

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	All Patients (*n = 1,879*)	Standard (*n = 476*)	Highly Adhesive (*n = 465*)	Chlorhexidine (*n = 938*)
Age, yr, median (IQR)	64 (53–75)	64 (53–74)	64 (52–76)	63.5 (53–74)
Male, n (%)	1,255 (66.8)	313 (65.8)	305 (65.6)	637 (67.9)
At least one chronic disease, n (%)	587 (31.2)	154 (32.4)	135 (29)	298 (31.8)
Immune deficiency, n (%)	91 (4.8)	28 (5.9)	16 (3.4)	47 (5)
Hematologic malignancy, n (%)	53 (2.8)	14 (2.9)	8 (1.7)	31 (3.3)
Metastatic cancer, n (%)	118 (6.3)	28 (5.9)	28 (6)	62 (6.6)
AIDS, n (%)	44 (2.3)	13 (2.7)	7 (1.5)	24 (2.6)
SAPS II, median (IQR)*	51 (37–67)	49 (36–66.5)	51 (36–67)	52 (39–68)
SOFA, median (IQR)†	8 (5–11)	8 (5–11)	8 (5–11)	8 (5–11)
Admission category, n (%)				
Medical	1,386 (73.8)	335 (70.4)	342 (73.5)	709 (75.6)
Scheduled surgery	150 (8)	35 (7.4)	45 (9.7)	70 (7.5)
Emergency surgery	343 (18.3)	106 (22.3)	78 (16.8)	159 (17)
Main reason for ICU admission, n (%)				
Septic shock	334 (17.8)	92 (19.3)	89 (19.1)	153 (16.3)
Cardiogenic shock	128 (6.8)	29 (6.1)	37 (8)	62 (6.6)
De novo respiratory failure	488 (26)	129 (27.1)	114 (24.5)	245 (26.1)
Coma	167 (8.9)	41 (8.6)	39 (8.4)	87 (9.3)
Trauma	114 (6.1)	35 (7.4)	23 (4.9)	56 (6)
Mechanical ventilation, n (%)	1,336 (71.1)	333 (70)	333 (71.6)	670 (71.4)
Length of ICU stay, d, median (IQR)	9 (5–20)	10 (5–20)	9 (5–18)	9 (5–20)
ICU death, n (%)	586 (31.2)	141 (29.6)	152 (32.7)	293 (31.2)

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

* Range of possible scores, 0–162.

† Range of possible scores, 0–24.

TABLE 2. CATHETER CHARACTERISTICS

Variable	All Catheters (*n* = *4,163*)	Standard (*n* = *1,067*)	Highly Adhesive (*n* = *988*)	Chlorhexidine (*n* = *2,108*)
Data for all vascular catheters				
Time in place, d, median (IQR)	6 (4–11)	7 (4–12)	6 (3–10)	6 (4–11)
Experience of the operator <50 procedures, n (%)	1,530 (36.8)	380 (35.6)	391 (39.6)	759 (36)
Antimicrobials at catheter insertion, n (%)	2,303 (55.3)	592 (55.5)	528 (53.4)	1,183 (56.1)
Transport to operating room with catheter in place, n (%)				
No	3,436 (82.5)	877 (82.2)	812 (82.2)	1,747 (82.9)
Once	587 (14.1)	148 (13.9)	140 (14.2)	299 (14.2)
Twice	94 (2.3)	24 (2.2)	25 (2.5)	45 (2.1)
More than twice	46 (1.1)	18 (1.7)	11 (1.1)	17 (0.8)
Transport out of ICU with catheter in place, n (%)				
No	2,638 (63.4)	675 (63.3)	632 (64)	1,331 (63.1)
Once	1,109 (26.6)	272 (25.5)	284 (28.7)	553 (26.2)
Twice	294 (7.1)	86 (8.1)	45 (4.6)	163 (7.7)
More than twice	122 (2.9)	34 (3.2)	27 (2.7)	61 (2.9)
Number of dressing changes per catheter, median (IQR)	2 (1–4)	3 (1–5)	2 (1–4)	2 (1–4)
Catheter removal for suspected infection, n (%)	563 (13.5)	155 (14.5)	130 (13.2)	278 (13.2)
Data for arterial catheters only				
Arterial catheter, n (%)	2,201 (52.9)	558 (52.3)	515 (52.1)	1,128 (53.5)
Femoral	773 (35.1)	207 (37.1)	173 (33.6)	393 (34.8)
Radial	1,428 (64.9)	351 (62.9)	342 (66.4)	735 (65.2)
Data for CVCs only				
All CVCs, n (%)	1,962 (47.1)	509 (47.7)	473 (47.9)	980 (46.5)
Jugular CVCs	728 (37.1)	180 (35.4)	175 (37)	373 (38.1)
Subclavian CVCs	567 (28.9)	152 (29.9)	140 (29.6)	275 (28.1)
Femoral CVCs	667 (34)	177 (34.8)	158 (33.4)	332 (33.9)
Guidewire exchange, n (%)	76 (3.9)	23 (4.5)	20 (4.2)	33 (3.4)
Tunneled catheters, n (%)	5 (0.3)	1 (0.2)	2 (0.4)	2 (0.2)
Venous catheter lumens, n (%)				
One	17 (0.9)	6 (1.2)	3 (0.6)	8 (0.8)
Two	201 (10.2)	50 (9.8)	42 (8.9)	109 (11.1)
Three	1,458 (74.3)	375 (73.7)	358 (75.7)	725 (74)
Greater than three	286 (14.6)	78 (15.3)	70 (14.8)	138 (14.1)
Use of lipids, n (%)	938 (47.8)	247 (48.5)	219 (46.3)	472 (48.2)
Use of heparin, n (%)	615 (31.3)	159 (31.2)	146 (30.9)	310 (31.6)
Red-blood-cell pack transfused, n (%)	766 (39)	201 (39.5)	182 (38.5)	383 (39.1)

Definition of abbreviations: CVC = central venous catheter; ICU = intensive care unit; IQR = interquartile range.

Skin Colonization

Count-Tact cultures were performed at removal of 2,965 catheters and were negative in 918 (31%) cases. Bacterial growth was more common in patients with colonization (89%), major-CRI (87.5%), or CR-BSI (87.5%) than in patients with noncolonized catheters (67.5%; $P < 0.001$). Median (IQR) rate of Count-Tact positivity was significantly lower in the chlorhexidine versus the nonchlorhexidine group and significantly higher in the highly adhesive nonchlorhexidine versus the standard group (23 [1–101] vs. 10 [0–100]; $P = 0.010$) (*see* Table E3).

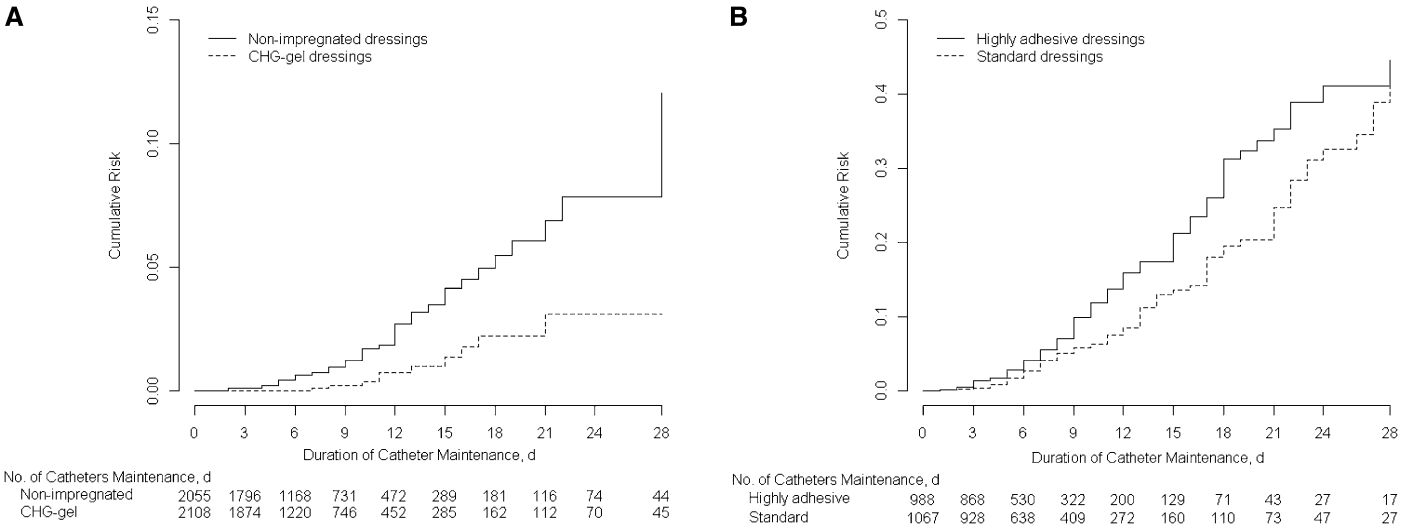

Figure 2. Cumulative risk of (*A*) major catheter-related infections (CRI) with chlorhexidine-gel (CHG) dressings and nonantiseptic dressings, and (*B*) catheter colonization with highly adhesive nonchlorhexidine dressings versus standard dressings.

TABLE 3. HAZARD RATIOS IN THE INTENTION-TO-TREAT ANALYSIS

Variable	Nonchlorhexidine vs. Chlorhexidine Dressings (*941 patients/2,055 catheters vs. 938 patients/2,108 catheters*)	Standard vs. Highly Adhesive Dressings (*476 patients/1,067 catheters vs. 465 patients/988 catheters*)
Catheter colonization		
Incidence (n per 1,000 catheter-days)	10.9 vs. 4.3	9.6 vs. 12.5
Hazard ratio	0.412 (0.306–0.556), $P < 0.0001$	1.651 (1.208–2.256), $P = 0.0016$
Catheter-related bloodstream infection		
Incidence (n per 1,000 catheter-days)	1.3 vs. 0.5	1.3 vs. 1.3
Hazard ratio	0.402 (0.186–0.868), $P = 0.02$	1.215 (0.470–3.142), $P = 0.689$
Major catheter-related infections		
Incidence (n per 1,000 catheter-days)	2.1 vs. 0.7	2.3 vs. 1.9
Hazard ratio	0.328 (0.174–0.619), $P = 0.0006$	1.052 (0.517–2.142), $P = 0.888$

Adverse Events

No systemic adverse reaction to chlorhexidine occurred. Severe contact dermatitis requiring permanent discontinuation of the study dressing occurred in 22 chlorhexidine-group patients (1.1 per 100 catheters), four highly adhesive-group patients (0.5 per 100 catheters), and one standard-group patient (0.1 per 100 catheters) ($P = 0.0005$ for comparison among the three groups, $P < 0.0001$ for comparison between chlorhexidine and nonchlorhexidine dressings, $P = 0.17$ for comparison between standard and highly adhesive nonchlorhexidine dressings).

Contact dermatitis usually occurred for a single catheter per patient and selectively affected patients with multiple organ failure, subcutaneous edema, and fragile skin. No systemic adverse reactions to chlorhexidine occurred.

The rate of abnormal International Contact Dermatitis Research Group scores was significantly higher with chlorhexidine (2.3%) than without chlorhexidine (1%; $P < 0.0001$). Abnormal scores were significantly more common with the highly adhesive dressing (1.4%) than with the standard dressing (0.7%; $P = 0.0039$).

DISCUSSION

A chlorhexidine-gel dressing placed at catheter insertion significantly reduced the risk of major-CRI by 67%, and the risk of CR-BSI by 60%, compared with nonantiseptic dressings. The high rate of dressing detachment decreased significantly with highly adhesive dressings, which increased skin and catheter colonization rates at catheter removal without affecting major-CRIs. Contact dermatitis with chlorhexidine dressings occurred for 1.1 per 100 catheters, a rate comparable with that reported with chlorhexidine sponges in similar patients in the ICU (13). Severe contact dermatitis requires early recognition followed by immediate chlorhexidine-dressing removal, although no systemic allergies occurred in our study.

With current continuous quality improvement programs based on care bundles, the major-CRI risk is less than 4% of catheters. Most of the measures recommended for CRI prevention were used in our study centers, in keeping with the low major-CRI rate in the nonchlorhexidine groups. Based on a large multicenter randomized trial (13) and a metaanalysis (26), a chlorhexidine-impregnated sponge (Biopatch; Ethicon) placed under a transparent polyurethane dressing is now recommended by the Centers for Disease Control and Prevention (grade IB) to decrease CLA-BSIs when basic prevention measures are inadequate (3). This sponge had a low contact-dermatitis rate of 5.3 per 1,000 catheters but was difficult to apply; furthermore, the sponge sometimes failed to contact the skin around the catheter insertion site if the fixation sutures for catheter were very near the entry point. Tegaderm CHG contains a transparent hydrophilic gel with 2% (wt/wt) CHG in a semipermeable transparent polyurethane dressing that prevents fluid accumulation and allows skin inspection. Studies showed similar antimicrobial activity of Tegaderm CHG compared with the chlorhexidine sponge, for up to 10 days (27). The chlorhexidine dressing decreased major-CRI and CR-BSI rates in our study similarly to the sponge (13). The rate of severe contact dermatitis was comparable with that reported with chlorhexidine sponges.

In our previous study (13), we used standard transparent Tegaderm dressings, of which two-thirds were replaced earlier than scheduled, because of soiling or detachment. Spontaneous dressing detachment was associated with catheter colonization and infection (28), suggesting that a highly adhesive transparent dressing (Tegaderm HP Transparent Film Dressing) might decrease catheter colonization and major-CRI rates. However, skin and catheter colonization rates at catheter removal were higher with Tegaderm HP, despite a significant decrease in early dressing changes. The hydrophilic acrylate component in Tegaderm HP may have resulted in skin toxicity or dermabrasion during dressing changes, increasing the risk of colonization from the pilosebaceous units.

Our study is the first to evaluate chlorhexidine-gel dressings for major-CRI prevention and the second large randomized controlled trial (after [13]) showing that chlorhexidine dressings decrease major-CRI and CR-BSI rates in ICUs. Nine out of the 12 ICUs never used chlorhexidine dressings. In addition, we obtained data from multiple medical and surgical ICUs from university and nonuniversity hospitals. Nearly all eligible patients were included, and few patients and catheters were lost to follow-up. Finally, all cases of suspected CRI or colonization were reviewed by a panel of masked assessors to ensure valid assessment of the primary endpoint. Therefore, our results can reasonably be generalized to all critically ill patients who are expected to need CVCs or arterial catheters for short periods.

Extensive use of chlorhexidine dressings carries a theoretical risk of selecting chlorhexidine-resistant organisms. However, prior work demonstrated that the chlorhexidine concentration remained greater than the minimum inhibitory concentrations of skin organisms for 7 days, and that chlorhexidine-gel dressings were effective against even the most resistant organisms (27). No evidence of a decrease in chlorhexidine susceptibility of colonizing bacteria was found in our earlier study (13).

Our study has several limitations. Double-masking was not feasible, because nonchlorhexidine-gel dressings were not available. However, a masked procedure was used for catheter cultures and independent assessors conducted a masked review of all suspected catheter infections. Major-CRI, particularly without bacteremia, may be difficult to diagnose. However, major-CRI was assessed by masked investigators, and results were similar when we used other endpoints, such as catheter colonization or CR-BSI. Importantly, although CLA-BSI might be difficult to accurately diagnose in the ICU, it also decreased the CLA-BSI rate (22). Catheter colonization might inaccurately reflect catheter infection. Furthermore, no cultures were obtained for 6.9% of catheters. However, colonization has been found to accurately correlate with CR-BSI (29) and is used as the primary endpoint in other recent randomized controlled trials (30, 31). Finally, either alcoholic PVI or 0.5% alcoholic chlorhexidine was used

for antisepsis in all centers because, unfortunately, aqueous or alcoholic 2% chlorhexidine was not commercially available in France during the study. However, the potential benefit of 2% chlorhexidine with or without alcohol versus 0.5% alcoholic chlorhexidine or 5% alcoholic PVI remains unclear (3).

In conclusion, a chlorhexidine-gel dressing decreased major-CRI rate in ICUs implementing a quality improvement program with care bundles. A highly adhesive dressing without antiseptic decreased the rate of dressing loosening but increased skin and catheter colonization without influencing catheter infections.

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