Chlorhexidine-Impregnated Sponges and Less Frequent Dressing Changes for Prevention of Catheter-Related Infections in Critically Ill Adults: A Randomized Controlled Trial

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PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT (ICU) usually require insertion of central venous catheters (CVCs). In Europe, the incidence density of CVC-related bloodstream infections ranges from 1 to 3.1 per 1000 patient-days.¹ In the United States, 15 million CVC-days are estimated to occur each year in ICU patients, as well as approximately 80 000

See also p 1285 and Patient Page.
CVC-related bloodstream infections.\textsuperscript{2,3} The attributable mortality of CVC-related bloodstream infections ranges from 0\% to 11.5\%, and the excess ICU length of stay resulting from these infections is estimated at 9 to 12 days.\textsuperscript{4,5} Consequently, efforts are required to decrease the incidence of these infections.

Several reports suggest that multiple preventive strategies should be implemented concomitantly. These interventions include staff education, maximal barrier precautions for catheter insertion, use of chlorhexidine for skin antisepsis, preferential use of the subclavian site for CVC insertion, prompt removal of unnecessary catheters, surveillance, and feedback.\textsuperscript{6,7} Implementation of such quality-improvement programs may decrease CVC-related bloodstream infection rates to less than 2 per 1000 CVC-days.\textsuperscript{8-10} Given these low rates, it is not clear whether new technical devices confer further advantages.\textsuperscript{2,11}

Most organisms responsible for CVC-related bloodstream infections originate from the insertion sites of short-term CVCs.\textsuperscript{12} Therefore, decreasing bacterial colonization of the skin at the insertion site may decrease the risk of bloodstream infection. New materials under development to decrease colonization include a chlorhexidine gluconate–impregnated sponge (CHGIS) (BioPatch; Ethicon Inc, Somerville, NJ) to be placed over the CVC insertion site. A meta-analysis of small or unpublished studies of the CHGIS has suggested a significant decrease in catheter colonization and a nonsignificant decrease in CVC-related bloodstream infections, indicating a need for a large randomized controlled trial.\textsuperscript{13}

Studies in recipients of bone marrow transplants found no evidence that increasing the time between CVC dressing changes induced adverse effects.\textsuperscript{14,15} No data exist to determine whether the interval between CVC dressing changes can be safely extended in other populations.

The aim of this study was to evaluate the respective effects of using CHGIS dressings and increasing the time between dressing changes in adult ICU patients. We hypothesized that CHGIS dressings would decrease the rate of major catheter-related infections (CRIs), defined as catheter-related sepsis with or without bloodstream infection, and that a longer time between dressing changes would not increase the rate of major CRIs.

**METHODS**

**Study Design**

We conducted a multicenter, 2 × 2 factorial, randomized controlled trial to compare CHGIS vs standard dressings and to compare a strategy of changing unsoiled adherent dressings every 7 days vs the standard practice of every 3 days. The study was not blinded for the investigators or ICU staff but was blinded for the microbiologists processing the skin and catheter cultures and for the assessors.

**Study Patients**

From December 20, 2006, to May 20, 2008, we recruited patients in 7 ICUs (2 medical, 2 surgical, 3 medical-surgical) in 3 university and 2 general hospitals in France. Patients older than 18 years expected to require an arterial catheter, central-vein catheter, or both inserted for 48 hours or longer were eligible. Patients with a history of allergy to chlorhexidine or to transparent dressings were excluded.

The study was approved by the ethics committee of the Grenoble University Hospital, Grenoble, France. Written informed consent was obtained from patients whose decision-making capacity was intact. In accordance with French law, the Grenoble University Hospital ethics committee approved delayed consent from patients unable to make decisions at the time of catheter insertion.\textsuperscript{16} Patients were randomly assigned to 1 of 4 treatment groups. The randomization schedule, stratified by ICU, was developed using a Web-based random-number generator to select permuted blocks of 8 patients each.

**Study Catheters**

All arterial catheters and CVCs in a given patient were managed in the same way. Pulmonary arterial, hemodialysis, and peripherally inserted CVCs were not included.

All study centers followed French recommendations for catheter insertion and care, which are similar to recommendations from the Centers for Disease Control and Prevention.\textsuperscript{17} Briefly, the insertion sites were the radial artery and subclavian vein whenever possible, unless using these sites carried an increased risk of noninfectious complications.\textsuperscript{18} Maximal sterile barrier precautions (large sterile drape; surgical hand antisepsis; and mask, cap, sterile gloves, and gown) were used at catheter insertion. The insertion site was scrubbed with 4\% aqueous povidone-iodine solution (Betadine Scrub; Viatris Pharmaceuticals, Mergignac, France), rinsed with sterile water, and dried with sterile gauze; an alcohol-based antisepic solution (5\% povidone-iodine in 70\% ethanol) (Betadine Alcohool-based Solution; Viatris) was then applied for at least 1 minute, and sterile drapes were placed around the site.

Antiseptic- or antibiotic-impregnated CVCs were not used in any of the study ICUs. The same semipermeable transparent dressings (Tegaderm; 3M Inc, St Paul, Minnesota) were used in all 4 treatment groups. The dressing was changed 24 hours after catheter insertion (day 1) and then every 3 days (day 4, day 7, etc) in the 3-day group and every 7 days (day 8, day 15, etc) in the 7-day group. Leakage or soiling prompted immediate dressing change. The alcohol-based povidone-iodine solution was used for skin antisepsis during dressing changes.

In the CHGIS group, the CHGIS dressing was applied to the entire skin surface at and around the insertion site. The semitransparent dressing was then applied. A new CHGIS was used at each dressing change.

Suspected contact dermatitis or skin allergy was confirmed by a dermatologist, and photographs were taken. The investigator could decide to permanently stop CHGIS use in patients with suspected skin intolerance. The independent data and safety monitoring committee was immediately alerted, as

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well as the French Drug Agency and the manufacturers of the dressing materials.

Patients underwent follow-up until 48 hours after ICU discharge. Catheters were immediately removed if no longer needed, usually before ICU discharge, or when a CRI was suspected. Catheter tips were cultured using a simplified quantitative broth dilution technique.\(^{19}\) In the few patients who needed to retain their CVCs (because of treatment requiring a CVC or unacceptable risk associated with insertion of a new CVC) after their ICU stay, the CVC was left in place and paired blood samples were drawn simultaneously via the catheter hub and from a peripheral venous site before ICU discharge for determination of the differential time to positivity.\(^{20}\)

For semiquantitative insertion-site cultures, the insertion site was sampled before catheter removal by pressing a nutritive trypticase-soy agar plate (Count-tact; Biomerieux, Crapone, France) on the skin for 5 seconds, centering the plate on the insertion site. The plate was sent to the local microbiology laboratory and cultured for 48 hours. The number of microorganisms recovered from the surface area corresponding to that of the CHGIS was counted.

The microbiology technicians and biologists in charge of the catheter and skin cultures were blinded to study group assignment. A random sample of 25 microorganisms recovered from skin cultures in each study group was processed for identification and determination of minimal bactericidal concentration (MBC), using a variant of a previously described method.\(^{21}\)

When major CRI was suspected, 1 or more peripheral blood samples were collected for culturing within 48 hours before or after catheter removal. If the catheter-tip culture revealed colonization or if a blood culture sampled at the time of catheter removal tested positive, an investigator blinded to the study group reviewed the case report form and medical chart to collect all of the available information needed to prepare an independent blinded review.

**Definitions and Primary Evaluation Criteria**

Three definitions were used, according to French\(^{37}\) and US\(^{22}\) guidelines. First, catheter colonization was defined as a quantitative catheter-tip culture yielding at least 1000 colony-forming units (CFUs)/mL. Second, catheter-related clinical sepsis without bloodstream infection was defined as a combination of (1) fever (body temperature ≥38.5°C) or hypothermia (body temperature ≤36.5°C), (2) a catheter-tip culture yielding at least 10^4 CFUs/mL, (3) pus at the insertion site or resolution of clinical sepsis after catheter removal, and (4) absence of any other infectious focus. Third, catheter-related bloodstream infection was defined as a combination of (1) 1 or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal, (2) a quantitative catheter-tip culture testing positive for the same microorganisms (same species and same susceptibility pattern) or a differential time to positivity of blood cultures greater than or equal to 2 hours, and (3) no other infectious focus explaining the positive blood culture result.\(^{20}\) If a patient had a blood culture testing positive for coagulase-negative staphylococci, the same pulsotype from the strains recovered from the catheter and blood culture was required for a diagnosis of catheter-related bloodstream infection.

We defined major CRI as either catheter-related clinical sepsis without bloodstream infection or catheter-related bloodstream infection. For the intention-to-treat analysis, the diagnosis of major CRI in patients with uncultured catheters was made by the independent blinded reviewers, who considered sepsis or bloodstream infection catheter-related when there was no other detectable cause of sepsis with or without bloodstream infection.

Catheter colonization was the primary evaluation criterion for assessing noninferiority of the 7-day dressing-change interval compared with the 3-day interval. The major CRI rate was the primary evaluation criterion for assessing differences between CHGIS and standard dressings. For the intention-to-treat analysis, uncultured catheters were classified as not colonized.

**Secondary Evaluation Criteria**

Secondary evaluation criteria were catheter-related bloodstream infection and skin colonization as assessed by the semiquantitative insertion-site skin culture at catheter removal.

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 (0, normal skin; 1, mild redness only; 2, red and slightly thickened skin; 3, intense redness and swelling with coalesced large blisters or spreading reaction).\(^{23}\)

**Number of Patients and Catheters**

The main assumptions were that CHGIS would lead to a 60% decrease in the major CRI rate from a 4% rate in the control group and that 12% of catheters would be colonized in both dressing-change interval groups.\(^{1,8}\) Noninferiority for the comparison of alternative dressing changes was defined as the upper limit of the 2-sided 95% confidence interval (CI) being less than 3 percentage points. Based on data from the study ICUs, we hypothesized that each patient would have at least 2 catheters inserted. We used α = .05 and 1 − β = .80 to compute sample size. We planned to enroll 1600 patients.

**Statistical Analysis**

The primary analysis was performed in the intention-to-treat population, which included all patients except those who withdrew their consent to participate, in accordance with French law. No interim analysis was planned. We also conducted a per-protocol analysis in which only cultured catheters were taken into account to compare 3-day vs 7-day dressing change intervals. For the comparison of CHGIS vs no CHGIS (control), we included uncultured cath-
etters if culturing for differential time to positivity was performed before catheter removal.

Characteristics of patients, catheters, and dressing is described as No. (%) or median (interquartile range [IQR]) for qualitative and quantitative variables and were compared between treatment groups using $\chi^2$ or Mann-Whitney tests, as appropriate. Kaplan-Meier curves of the risk of major CRIs 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 equating the patient), we used a marginal Cox model for patient, using a robust sandwich covariance estimate (PROC PHREG of SAS version 9.1; SAS Institute Inc, Cary, North Carolina). Analyses were stratified by ICU. The design of this factorial study assumed that the study interventions did not interact. This assumption was confirmed by testing for a treatment interaction in the Cox model. Accordingly, we analyzed the CHGIS effect (vs control) and the 7-day dressing change interval effect (vs 3-day dressing interval) separately (at the margins), using similar techniques. We checked the proportional hazards assumption and looked for qualitative interactions between treatment effects and among treatment centers.

To test noninferiority of the 7-day interval vs the 3-day interval between dressing changes, the 2-sided 95% CI was calculated for the true difference in the rate of significant catheter colonization. Noninferiority was defined as the upper limit of the 2-sided 95% CI being less than 3 percentage points. Tests were 2-tailed and unadjusted for multiple comparisons. According to previous recommendations, we performed a sensitivity analysis of the final result while making the assumption that all uncultured catheters were colonized, using the per-protocol population and various subpopulations.

In this analysis, we tested noninferiority for 7-day dressing changes in the per-protocol population, arterial catheters only, venous catheters only, catheters in place at least 5 days, catheters with more than 1 unplanned dressing change, and catheters with at least 2 unplanned dressing changes.

Skin cultures were classified into 4 groups: sterile, less than 1 log$_{10}$ CFUs/plate, 1 to 2 log$_{10}$ CFUs/plate, and greater than 2 log$_{10}$ CFUs/plate. A Cochran-Armitage test for trend was used to compare skin colonization according to the evaluation criterion studied. The number of CFUs recovered from skin cultures and the MBCs with and without chlorhexidine were compared using a Mann-Whitney test.

Analyses were performed using SAS version 9.1 and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). $P < .05$ was considered statistically significant.

### RESULTS

#### Patients and Catheters

Of 2095 patients with at least 1 catheter, 1653 were enrolled, but 17 subsequently withdrew consent to participate, leaving 1636 available for inclusion in the intention-to-treat analysis (FIGURE 1), for a total of 3778 catheters and 28931 catheter-days. Patient and catheter characteristics are reported in TABLE 1 and TABLE 2.

In the reference group treated without CHGIS dressings and with 3-day dressing changes, the catheter colonization rate was 11.5% (99 events, 15.8 per 1000 catheter-days), the major CRI rate was 1.2% (10 events, 1.6 per 1000 catheter-days), and the catheter-related bloodstream infection rate was 0.9% (8 events, 1.28 per 1000 catheter-days).

Semiquantitative insertion-site cultures were performed at removal of 2903 of 3778 catheters. There were no organisms in 1887 cases (65%). Higher median semiquantitative culture counts were associated with colonization (not colonized, 0 [IQR, 0-0]; range, 0 to 10$^6$ CFUs/plate vs colonized, 40 [IQR, 0-100]; range, 0 to 10$^7$ CFUs/plate); $P < .001$) and major CRI (no major CRI, 0 [IQR, 0-1; range, 0 to 10$^6$ CFUs/plate] vs major CRI, 50 [IQR, 0-100]; range, 0 to 10$^7$ CFUs/plate); $P < .001$).

Of the 12882 dressing changes, 5808 (45%) were performed before the planned date because of soiling or leakage. For 1727 arterial catheters, premature dressing changes were more common at the femoral artery (1242/2333 [53.2%]) than at the radial artery (1626/3458 [47.0%]) ($P < .001$). For 2051 CVCs, premature dressing changes were more common at the jugular and femoral veins (1950/4177 [46.7%]) than at the subclavian vein (990/2914 [34.0%]) ($P < .001$).

In the 3-day group, 2652 of 6597 dressing changes (40%) were unplanned. In this group, 639 catheters (37%) were in place for at least 3 days, with no unplanned dressing changes. In the 7-day group, 3156 of 6285 dressing changes (50%) were unplanned. In this group, 200 catheters (10%) were in place for at least 7 days, with no unplanned dressing changes. The skin was considered free from evidence of contact dermatitis at 12717 changes (98.7%). Mild redness was noted at 133 changes (1%), red and slightly thickened skin at 25 changes, and more intense reactions at 5 changes.

There was no significant interaction between the 2 study interventions regarding the rates of catheter colonization ($P = .53$), major CRI ($P = .19$), or catheter-related bloodstream infection ($P = .36$).

### CHGIS Dressings vs Control Dressings

Use of CHGIS dressings decreased the major CRI rate from 1.40 per 1000 catheter-days to 0.60 per 1000 catheter-days (hazard ratio [HR], 0.39; 95% CI, 0.17-0.93; $P = .03$) (FIGURE 2). Use of CHGIS dressings significantly decreased the rates of catheter colonization and catheter-related bloodstream infections (TABLE 3). The effect was similar for gram-negative and gram-positive organisms (TABLE 4) and for arterial catheters and CVCs. Based on these results, use of CHGIS dressings was estimated to prevent 1 major CRI for every 117 catheters (95% CI, 86-
1020 catheters) left in place for a mean duration of 10 days.

The semiquantitative culture count was significantly lower in the CHGIS group (Table 5). The MBC of chlorhexidine was determined for 106 strains cultured from the skin at catheter removal. The median MBC was not different between the control and CHGIS groups (4 [IQR, 4–16] vs 4 [IQR, 4–8], respectively; \(P = .30\)). The MBC of chlorhexidine was greater than 32 in 4 of 52 control-group strains (Enterococcus faecalis [2], E faecium [1], Providencia stuartii [1]) and 5 of 54 CHGIS-group strains (E faecalis [4], Pseudomonas aeruginosa [1]).

**Adverse Events**

Severe contact dermatitis leading to permanent removal of the CHGIS occurred in 8 patients (10 catheters [10.4 per 1000 patients and 5.3 per 1000 catheters]). The rate of abnormal scores according to the International Contact Dermatitis Research Group system was significantly higher in the CHGIS group (100/6720 [1.49%]) than in the control group (63/5875 [1.02%]) \(P = .02\). Contact dermatitis usually occurred for only 1 catheter per patient and selectively affected very sick patients with multiple organ failures, subcutaneous edema, and fragile skin. No systemic adverse reactions to chlorhexidine occurred. Skin allergy to the semipermeable transparent dressing was diagnosed in 2 patients (1 in the CHGIS group, 1 in the control group); the lesions resolved after dressing removal.

**3-Day vs 7-Day Dressing Changes**

In the 3-day group, 2652 of 6597 dressing changes (40%) were unplanned. In this group, 639 catheters (37%) were in place for at least 3 days, with no unplanned dressing changes. In the 7-day group, 3156 of 6285 dressing changes (50%) were unplanned. In this group, 200 catheters (10%) were in place for at least 7 days, with no unplanned dressing changes. The median number of dressing changes was significantly higher in the 3-day group (0.46 [IQR, 0.33–0.63] per catheter-day) than in the 7-day group (0.40 [IQR, 0.25–0.60] per catheter-day) \(P < .001\). The rate of premature dressing changes was significantly lower in the 3-day group than in the 7-day group (40.2% [2652/6597] vs 50.6% [3156/6285], \(P < .001\)).

The rate of catheter colonization (primary criterion) was 7.8% (142 events, 10.4 per 1000 catheter-days) in the 3-day group and 8.6% (168 events, 11.0 per 1000 catheter-days) in the 7-day group (Table 3 and Figure 2). The HR was 0.99 (95% CI, 0.77–1.28) (absolute difference in the rate of significant catheter colonization, 0.8% [95% CI, −1.78% to 2.15%]). Thus, the 7-day dressing changes met the prespecified criteria for noninferiority, compared with the 3-day dressing changes. The estimated HR was similar for CVCs (0.94 [95% CI, 0.70–1.27]) and arterial catheters (1.07 [95% CI, 0.75–1.53]).

In the sensitivity analyses, results were inconclusive for arterial catheters only and for catheters with at least 2 unplanned dressing changes. Otherwise, the sensitivity analyses were consistent with noninferiority. In particular, the absolute difference in the rate of significant catheter colonization was 0.6% (95% CI, −1.97% to 2.37%) in the per-protocol population.

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**Figure 1. Flow of Patients Through the Study**

CHGIS indicates chlorhexidine gluconate–impregnated sponge; DTP, differential time to positivity; ICU, intensive care unit.

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CHLORHEXIDINE-IMPREGNATED SPONGES AND CATHETER-RELATED INFECTIONS

In the subgroup of 2416 catheters left in place for at least 5 days, the catheter colonization rate in the 3-day group was 9.8% (114 events; 9.7 per 1000 catheter-days) vs 10.8% in the 7-day group (135 events; 10.3 per 1000 catheter-days) (HR, 0.98 [95% CI, 0.74-1.30]; P = .88). The median number of dressing changes per catheter was higher in the 3-day group (4 [IQR, 3-6]) than in the 7-day group (3 [IQR, 2-5]) (P < .001). The median number of dressing changes per catheter-day was 0.43 (IQR, 0.33-0.60) in the 3-day group and 0.37 (IQR, 0.25-0.55) in the 7-day group, a 14% decrease.

There was a slight but statistically significant trend for higher skin colonization counts by semiquantitative skin culture at catheter removal in the 7-day group compared with the 3-day group (Table 5). The number of major CRIs was 12.06 (per 1000 catheter-days) in the 3-day group and 17.08 (per 1000 catheter-days) in the 7-day group (HR, 1.16 [95% CI, 0.49-2.69]; P = .74; difference, 0.21% [95% CI, −0.33% to 1.11%]).

COMMENT

We found that use of CHGIS dressings decreased the risk of major catheter-related infections by 60% despite a low baseline infection rate. The incidence of skin lesions with the CHGIS dressings was lower than that in prior reports; but contact dermatitis will occur occasionally and requires prompt removal of the CHGIS. We also found that a strategy of weekly scheduled dressing changes for nonsoiled, adherent dressings was not inferior to a standard 3-day dressing change. However, unscheduled dressing changes for soiling and leakage were common, and the absolute reduction in number of dressing changes was modest.

Most of the measures recommended for preventing CRI were used in our study centers, in keeping with the low rate of major CRI in the 3-day control group without CHGIS dressings. This low baseline rate is noteworthy, given the inclusion of severely ill patients, as shown by the high Simplified Acute Physiology Score II and Sequential Organ Failure Assessment scores at ICU admission and the large proportion of ventilated patients. The baseline rate was less than the predicted 4% rate used to compute the sample size for establishing the superiority of CHGIS dressings. Fortunately, the sample size required for demonstrating noninferiority of the 7-day dressing-change interval compared with the 3-day interval was large, so we had enough patients to establish the superiority of CHGIS dressings over standard dressings for decreasing major CRI rates.

Most studies of devices designed to decrease CRI (eg, antiseptic- or antibiotic-impregnated catheters) were performed in ICUs in which baseline CRI rates were at the higher end of the reported range. In this setting, simple preventive measures may be as effective as new devices. Thus, the 2002 guidelines from the Centers for Disease Control and Prevention recommend antiseptic- or antibiotic-impregnated catheters only in ICUs in which catheter-related infection rates are above benchmark rates despite implementation of a comprehensive strategy to decrease the rates. We found that the CHGIS was effective in decreasing major CRI, despite low baseline infection rates. Our results therefore suggest that technical devices as well as a set of simple preventive measures may be useful for preventing major CRIs in ICUs.

A randomized study comparing dressings every 4 days and every 15 days in children undergoing chemotherapy found no differences in the rates of positive skin culture results or bloodstream infections. Another study in re-
recipients of bone marrow transplants found that dressing changes every other day were associated with significantly greater skin toxicity than were changes every 5 or 10 days.\textsuperscript{15} Neither study was conducted in ICUs. The catheter colonization rate in our study was not different in patients with dressing changes every 3 days or every 7 days. Neither were the rates of major CRI or catheter-related bloodstream infections significantly different between the groups. Extending the theoretical dressing change interval from 3 to 7 days resulted in only a 9\% decrease in the number of changes per catheter-day. However, the interval between changes decreased the number of changes by 14\% for catheters left in place for more than 4 days.

One possibility is that dressing changes during the study were performed even when minimal separation occurred. The small actual increase in dressing change intervals in our 7-day group indicates that extending the interval between dressing changes was not significantly better than dressing every 3 days.

### Table 2. Catheter Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Catheters, ITT Analysis (N = 3778)</th>
<th>Dressing Control (n = 1825)</th>
<th>CHGIS (n = 1953)</th>
<th>3d (n = 1815)</th>
<th>7d (n = 1963)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in place, median (IQR), d</td>
<td>6 (4-10)</td>
<td>6 (4-10)</td>
<td>6 (4-10)</td>
<td>6 (4-10)</td>
<td>6 (4-10)</td>
</tr>
<tr>
<td>Experience of the operator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 procedures</td>
<td>2586 (68.4)</td>
<td>1221 (66.9)</td>
<td>1365 (69.9)</td>
<td>1248 (68.7)</td>
<td>1338 (68.2)</td>
</tr>
<tr>
<td>≥50 procedures</td>
<td>1135 (30.1)</td>
<td>578 (31.7)</td>
<td>557 (28.5)</td>
<td>544 (30)</td>
<td>591 (30.1)</td>
</tr>
<tr>
<td>Junior operator with help from a senior</td>
<td>57 (1.5)</td>
<td>26 (1.4)</td>
<td>31 (1.6)</td>
<td>23 (1.3)</td>
<td>34 (1.7)</td>
</tr>
<tr>
<td>Arterial catheter</td>
<td>1727 (45.7)</td>
<td>830 (45.5)</td>
<td>897 (45.9)</td>
<td>821 (45.2)</td>
<td>906 (46.2)</td>
</tr>
<tr>
<td>Femoral</td>
<td>708 (41)</td>
<td>355 (42.8)</td>
<td>353 (39.4)</td>
<td>345 (42)</td>
<td>363 (40)</td>
</tr>
<tr>
<td>Radial</td>
<td>1019 (59)</td>
<td>475 (57.2)</td>
<td>544 (60.6)</td>
<td>476 (58)</td>
<td>543 (60)</td>
</tr>
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<td>Venous Catheters Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous catheter</td>
<td>2051 (54.3)</td>
<td>995 (54.5)</td>
<td>1056 (54.1)</td>
<td>994 (54.8)</td>
<td>1057 (53.8)</td>
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<tr>
<td>Jugular</td>
<td>560 (27.3)</td>
<td>248 (24.9)</td>
<td>312 (29.6)</td>
<td>272 (27.4)</td>
<td>298 (27.3)</td>
</tr>
<tr>
<td>Subclavian</td>
<td>819 (39.9)</td>
<td>407 (40.9)</td>
<td>412 (39.3)</td>
<td>390 (39.2)</td>
<td>429 (40.6)</td>
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<tr>
<td>Femoral</td>
<td>672 (32.8)</td>
<td>340 (34.2)</td>
<td>353 (39.4)</td>
<td>345 (42)</td>
<td>363 (40)</td>
</tr>
<tr>
<td>Guidewire exchange</td>
<td>85 (4.1)</td>
<td>28 (2.8)</td>
<td>57 (5.4)</td>
<td>47 (4.7)</td>
<td>38 (3.6)</td>
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<tr>
<td>No. of lumens in venous catheters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (1.8)</td>
<td>21 (2.1)</td>
<td>16 (1.5)</td>
<td>17 (1.7)</td>
<td>20 (1.9)</td>
</tr>
<tr>
<td>2</td>
<td>209 (10.2)</td>
<td>110 (11.1)</td>
<td>99 (9.4)</td>
<td>109 (11)</td>
<td>100 (9.5)</td>
</tr>
<tr>
<td>3</td>
<td>1805 (88)</td>
<td>864 (86.8)</td>
<td>941 (89.1)</td>
<td>868 (87.3)</td>
<td>937 (88.6)</td>
</tr>
<tr>
<td>Use of lipids</td>
<td>777 (37.9)</td>
<td>379 (38.3)</td>
<td>398 (37.7)</td>
<td>389 (39.2)</td>
<td>388 (36.7)</td>
</tr>
<tr>
<td>Use of heparin</td>
<td>706 (34.5)</td>
<td>336 (33.8)</td>
<td>372 (35.3)</td>
<td>341 (34.3)</td>
<td>367 (34.7)</td>
</tr>
<tr>
<td>Packaged red blood cells transfused</td>
<td>602 (29.4)</td>
<td>266 (26.7)</td>
<td>336 (31.8)</td>
<td>283 (28.5)</td>
<td>319 (30.2)</td>
</tr>
<tr>
<td>Tunneled catheters</td>
<td>6 (0.3)</td>
<td>5 (0.5)</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Antimicrobials at catheter insertion</td>
<td>2532 (67)</td>
<td>1208 (66.2)</td>
<td>1324 (67.8)</td>
<td>1199 (66.1)</td>
<td>1333 (67.9)</td>
</tr>
<tr>
<td>Transport with catheter(s) in place\textsuperscript{a}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3004 (79.5)</td>
<td>1448 (79.3)</td>
<td>1566 (79.7)</td>
<td>1431 (78.8)</td>
<td>1573 (80.1)</td>
</tr>
<tr>
<td>1</td>
<td>559 (14.8)</td>
<td>255 (14.4)</td>
<td>304 (15.5)</td>
<td>277 (15.3)</td>
<td>282 (14.4)</td>
</tr>
<tr>
<td>2</td>
<td>160 (4.2)</td>
<td>90 (4.9)</td>
<td>70 (3.6)</td>
<td>78 (4.3)</td>
<td>82 (4.2)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>55 (1.5)</td>
<td>32 (1.8)</td>
<td>23 (1.2)</td>
<td>29 (1.6)</td>
<td>26 (1.3)</td>
</tr>
<tr>
<td>No. of dressing changes per catheter, median (IQR)</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Local signs at catheter removal Normal</td>
<td>3416 (90.4)</td>
<td>1666 (91.3)</td>
<td>1750 (89.6)</td>
<td>1648 (90.8)</td>
<td>1768 (90.1)</td>
</tr>
<tr>
<td>Redness</td>
<td>321 (8.5)</td>
<td>139 (7.6)</td>
<td>182 (9.3)</td>
<td>150 (8.3)</td>
<td>171 (8.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>10 (0.3)</td>
<td>2 (0.1)</td>
<td>8 (0.4)</td>
<td>7 (0.4)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Nonpurulent discharge</td>
<td>42 (1.1)</td>
<td>20 (1.1)</td>
<td>22 (1.1)</td>
<td>18 (1)</td>
<td>24 (1.2)</td>
</tr>
<tr>
<td>Purulent discharge</td>
<td>15 (0.4)</td>
<td>6 (0.3)</td>
<td>9 (0.5)</td>
<td>6 (0.3)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Catheter removal for suspected infection</td>
<td>667 (17.7)</td>
<td>325 (17.8)</td>
<td>342 (17.5)</td>
<td>325 (17.6)</td>
<td>342 (17.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CHGIS, chlorhexidine gluconate-impregnated sponge; IQR, interquartile range; ITT, intention-to-treat.\textsuperscript{a} Transport of patient for imaging studies or surgery with the catheter in place.
interval to 7 days requires that the dressings be monitored closely and changed in the event of soiling or separation.

Use of CHGIS dressings was effective in decreasing major CRI. The effect size was similar for the primary end point, ie, major CRI, and the secondary end point, ie, catheter colonization. Our results confirm those of several studies performed in neonatal ICUs,28 adult ICUs, or hematology units.31 A meta-analysis showed a significant decrease in catheter-related bloodstream infection rates, possibly because of the small sample size and differences across included studies.13

Chlorhexidine gluconate is a critical component of interventions designed to prevent the dissemination of nosocomial infections.12 In vitro studies suggest that chlorhexidine exposure may cause reduced susceptibility to antibiotics and biocides via intrinsic or acquired mechanisms of resistance.33 At present, insufficient scientific evidence exists to evaluate these risks, and additional studies are needed. However, in keeping with previous studies,34,35 we found no evidence of bacterial resistance to chlorhexidine. Moreover, chlorhexidine concentrations beneath the dressing remain substantially higher than the concentrations that might promote the development of resistant strains for more than 7 days.35

Our randomized study is the largest to date evaluating dressings incorporating a CHGIS for prevention of major CRI. In addition, it was a multicenter study with a mix of medical and surgical ICUs in university and non-university hospitals. Furthermore, nearly all of the eligible patients were included, and few patients and catheters were lost to follow-up. All cases of suspected CRI or colonization were reviewed by a panel of blinded assessors to ensure valid assessment of the primary end point. Therefore, our results can reasonably be generalized to

Figure 2. Cumulative Risk of Catheter-Related Infection and Catheter Colonization

Median duration of catheterization was 6 days (interquartile range, 4-10 days) for all curves. y-Axis in blue indicates values in the range of 0-0.05. CHGIS indicates chlorhexidine gluconate-impregnated sponge; CI, confidence interval; HR, hazard ratio.

Table 3. Hazard Ratios in the Intention-To-Treat and Per-Protocol Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Catheter colonization &gt;10 CFUs/plate</th>
<th>Catheter-related bloodstream infection</th>
<th>Major catheter-related infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, No./1000 Catheter-Days</td>
<td>ITT Analysis</td>
<td>Per-Protocol Analysis</td>
</tr>
<tr>
<td></td>
<td>Control (n = 1825)</td>
<td>CHGIS (n = 1953)</td>
<td>Control (n = 1815)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>.03 (.28-0.46)</td>
<td>&lt;.001</td>
<td>.03 (.27-0.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td>.35 (.27-0.45)</td>
<td></td>
<td>10.4</td>
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<td></td>
<td></td>
<td></td>
<td>11.0</td>
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<td></td>
<td></td>
<td></td>
<td>.99 (.77-1.28)</td>
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<td></td>
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<td></td>
<td>.96 (.77-1.28)</td>
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<td>.99 (.77-1.28)</td>
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<td></td>
<td></td>
<td></td>
<td>.96 (.77-1.28)</td>
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<tr>
<td></td>
<td>.04 (.09-0.65)</td>
<td>.005</td>
<td>.04 (.09-0.63)</td>
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<td></td>
<td></td>
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<td>.004</td>
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<td></td>
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<td></td>
<td></td>
<td>.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.26 (.47-3.43)</td>
</tr>
<tr>
<td></td>
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<td>.65 (.48-3.40)</td>
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<td>1.28 (.48-3.40)</td>
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<td>.62</td>
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<tr>
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<td>.03 (.16-0.93)</td>
<td>.03</td>
<td>.03 (.16-0.92)</td>
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<td>.03</td>
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<td>.9</td>
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<td></td>
<td></td>
<td></td>
<td>1.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.16 (.50-2.68)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.74 (.51-2.73)</td>
</tr>
</tbody>
</table>

Abbreviations: CFU, colony-forming unit; CHGIS, chlorhexidine gluconate-impregnated sponge; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

*Analysis adjusted on imbalanced parameters (ie, presence of ≤1 chronic disease for comparison of control and CHGIS groups).
all severely ill ICU patients expected to require CVCs for short periods. Skin cultures samples obtained before catheter removal showed a significant decrease in bacterial skin colonization with CHGIS dressings compared with controls. The rates of catheter colonization and major CRI correlated significantly with the burden of bacterial skin contamination. These data support the biologically plausible mechanism of action of CHGIS. We detected no change in the profile of microorganisms recovered from skin samples and colonized catheters. An increase in the MBCs of the most resistant strains cannot be completely excluded, however, and studies of larger bacteriological samples are needed to further investigate this point.

The number needed to treat with CHGIS dressings was 117 catheters (95% CI, 86-1020). Treatment for 10 days usually requires 3 dressings, each of which costs US $6 (2007 dollars), and the cost of preventing a single episode of major CRI can be estimated at $2106 (95% CI, $1518-$18 360). The cost of managing a single episode of major CRI ranges from $8000 to more than $28 000,36 suggesting that CHGIS dressings may be cost saving.

Our study has several limitations. First, double-blinding was not feasible, because visually identical sponges without chlorhexidine were not available and the nurses had to be informed of the dressing change interval. However, a blinded procedure was used for the catheter cultures. Most importantly, independent assessors conducted a blind review of all suspected catheter infections.

Second, major CRI, particularly without bacteremia, may be difficult to diagnose, most notably in ICU patients. However, major CRI was assessed by investigators blinded to the study group, and the results were similar when we used other end points such as catheter colonization or catheter-related bloodstream infection.

Third, 6.5% of catheters were not cultured, either because the patients left the ICU with the CVCs in place or because technical problems arose. This rate compares favorably with rates from the largest randomized studies on the prevention of CRIs.10,37

Fourth, alcohol-based povidone iodine was used for skin antisepsis and catheter dressings in all centers. Chlorhexidine has been found more effective than a single application of non–alcohol-based povidone iodine,17,36,39 and the use of chlorhexidine for skin antisepsis is included in recommendations for preventing CRI. Unfortunately, aqueous 2% chlorhexidine was not commercially available in France at the beginning of our study. Furthermore, alcohol-based povidone iodine has been shown more effective than non–alcohol-based povidone iodine in decreasing catheter colonization in ICUs,40 and no study compared alcohol-based povidone iodine with chlorhexidine in aqueous or alcohol-based solution. Nevertheless, using chlorhexidine for skin antisepsis might have further reduced CRI rates in the control group.

In conclusion, the interval between dressing changes can be safely ex-
tended to more than 3 days but not exceeding 7 days, provided the dressings are closely monitored and changed immediately should separation or soiling be detected. Furthermore, use of CHGIS dressings decreases the rate of major CRI when the baseline rate is lower than 2 per 1000 catheter-days.

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Acquisition of data: Timsit, Schwebel, Bouadma, Geoffroy, Garrouste-Orgeas, Pease, Herault, Haouache, Calvino-Gunther, Gestin, Armand-Lefevre, Chaplain, Benali, Croize.

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Drafting of the manuscript: Timsit, Pease, Calvino-Gunther, Lucet.

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Statistical analysis: Calvino-Gunther, Francois.

Obtained funding: Timsit.

Administrative, technical, or material support: Timsit, Lucet.

Study supervision: Timsit, Schwebel, Armand-Lefevre, Zahar, Lucet.

Dr Schwabe and Bouadma contributed equally to the study.

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REFERENCES


Ideas come when we do not expect them, and not when we are brooding and searching at our desks. Yet ideas would certainly not come to mind had we not brooded at our desks and searched for answers with passionate devotion.

—Max Weber (1864-1920)