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

Jean-François Timsit, MD, PhD
Carole Schwebel, MD, PhD
Lila Bouadma, MD
Arnaud Geoffroy, MD
Maïté Garrouste-Orgeas, MD
Sebastian Pease, MD
Maïté Garrouste-Orgeas, MD
Hakim Haouache, MD
Silvia Calvino-Gunther, RN
Brieuc Gestin, PhD
Laurence Armand-Lefevre, PharmD
Véronique Leflon, PharmD
Chantal Chaplain, PharmD
Adel Benali, MD
Adrien Francais, MSc
Christophe Adrie, MD, PhD
Jean-Ralph Zahar, MD
Marie Thuong, MD
Xavier Arrault, PharmD
Jacques Croize, PharmD
Jean-Christophe Lucet, MD, PhD
for the Dressing Study Group

Context
Use of a chlorhexidine gluconate–impregnated sponge (CHGIS) in intravascular catheter dressings may reduce catheter-related infections (CRIs). Changing catheter dressings every 3 days may be more frequent than necessary.

Objective
To assess superiority of CHGIS dressings regarding the rate of major CRIs (clinical sepsis with or without bloodstream infection) and noninferiority (less than 3% colonization-rate increase) of 7-day vs 3-day dressing changes.

Design, Setting, and Patients
Assessor-blind, 2 × 2 factorial, randomized controlled trial conducted from December 2006 through June 2008 and recruiting patients from 7 intensive care units in 3 university and 2 general hospitals in France. Patients were adults (>18 years) expected to require an arterial catheter, central-vein catheter, or both inserted for 48 hours or longer.

Interventions
Use of CHGIS vs standard dressings (controls). Scheduled change of unsoiled adherent dressings every 3 vs every 7 days, with immediate change of any soiled or leaking dressings.

Main Outcome Measures
Major CRIs for comparison of CHGIS vs control dressings; colonization rate for comparison of 3- vs 7-day dressing changes.

Results
Of 2095 eligible patients, 1636 (3778 catheters, 28,931 catheter-days) could be evaluated. The median duration of catheter insertion was 6 (interquartile range [IQR], 4-10) days. There was no interaction between the interventions. Use of CHGIS dressings decreased the rates of major CRIs (10/1953 [0.5%], 0.6 per 1000 catheter-days vs 19/1825 [1.1%], 1.4 per 1000 catheter-days; hazard ratio [HR], 0.39 [95% confidence interval [CI], 0.17-0.93]; P = .03) and catheter-related bloodstream infections (6/1953 catheters, 0.40 per 1000 catheter-days vs 17/1825 catheters, 1.3 per 1000 catheter-days; HR, 0.24 [95% CI, 0.09-0.65]). Use of CHGIS dressings was not associated with greater resistance of bacteria in skin samples at catheter removal. Severe CHGIS-associated contact dermatitis occurred in 8 patients (5.3 per 1000 catheters). Use of CHGIS dressings prevented 1 major CRI per 117 catheters. Catheter colonization rates were 142 of 1657 catheters (7.8%) in the 3-day group (10.4 per 1000 catheter-days) and 168 of 1828 catheters (8.6%) in the 7-day group (11.0 per 1000 catheter-days), a mean absolute difference of 0.8% (95% CI, -1.78% to 2.15%) (HR, 0.99; 95% CI, 0.77-1.28), indicating noninferiority of 7-day changes. The median number of dressing changes per catheter was 4 (IQR, 3-6) in the 3-day group and 3 (IQR, 2-5) in the 7-day group (P < .001).

Conclusions
Use of CHGIS dressings with intravascular catheters in the intensive care unit reduced risk of infection even when background infection rates were low. Reducing the frequency of changing unsoiled adherent dressings from every 3 days to every 7 days modestly reduces the total number of dressing changes and appears safe.

Trial Registration
clinicaltrials.gov Identifier: NCT00417235

©2009 American Medical Association. All rights reserved.
(Reprinted) JAMA, March 25, 2009—Vol 301, No. 12 1231
CHLORHEXIDINE-IMPREGNATED SPONGES AND CATHETER-RELATED INFECTIONS

CVC-related bloodstream infections.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.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.6,7 Implementation of such quality improvement programs may decrease CVC-related bloodstream infection rates to less than 2 per 1000 CVC-days.8–10 Given these low rates, it is not clear whether new technical devices confer further advantages.2,11

Most organisms responsible for CVC-related bloodstream infections originate from the insertion sites of short-term CVCs.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.13

Studies in recipients of bone marrow transplants found no evidence that increasing the time between CVC dressing changes induced adverse effects.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 (CRLs), 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 CRLs.

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.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.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.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 antiseptic solution (5% povidone-iodine in 70% ethanol) (Betadine Alcoholf-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
CHLORHEXIDINE-IMPREGNATED SPONGES AND CATHETER-RELATED INFECTIONS

Definitions and Primary Evaluation Criteria
Three definitions were used, according to French and US guidelines. First, catheter colonization was defined as a quantitative catheter-tip culture yielding at least 10^3 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 10^3 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 that explains the positive blood culture result. If a patient had a blood culture testing positive for coagulase-negative staphylococci, the same pulstype 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 based 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).

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. 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-

©2009 American Medical Association. All rights reserved.
eters if culturing for differential time to positivity was performed before catheter removal.

Characteristics of patients, catheters, and dressings are described as No. (%) or median (interquartile range [IQR]) for qualitative and quantitative variables and were compared between treatment groups using χ² 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 (with the cluster equaling the 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 2 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 log₁₀ CFUs/plate, 1 to 2 log₁₀ CFUs/plate, and greater than 2 log₁₀ 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 28,931 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 10⁷ CFUs/plate; vs colonized, 40 [IQR, 0-100]; range, 0 to 10⁷ CFUs/plate; P < .001) and major CRI (no major CRI, 0 [IQR, 0-1; range, 0 to 10⁰ CFUs/plate] vs major CRI, 50 [IQR, 0-100; range, 0 to 10⁷ CFUs/plate]; P < .001).

Of the 12,882 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 (1626/3458 [47.0%]) vs control (1242/2333 [53.2%]) (P < .001). For 2051 CVCs, premature dressing changes were more common at the jugular and femoral veins (1950/4177 [46.7%]) vs at the subclavian vein (1709/3709 [45.9%]) (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 12,717 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.

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

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

©2009 American Medical Association. All rights reserved. (Reprinted) JAMA, March 25, 2009—Vol 301, No. 12 1235
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-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 (0.66 per 1000 catheter-days) in the 3-day group and 17 (0.87 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,28,29 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.3,30 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.14 Another study in re-
cipients 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.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. However, more than half of the catheters were removed before day 6, and approximately 40% of dressing changes were related to separation of the dressing from the skin. 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 was not effective.

### Table 2. Catheter Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Catheters, ITT Analysis (N = 3778)</th>
<th>Control (n = 1825)</th>
<th>CHGIS (n = 1953)</th>
<th>3 d (n = 1815)</th>
<th>7 d (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</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 (28.2)</td>
<td>353 (28.4)</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>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Femoral</td>
<td>672 (32.8)</td>
<td>340 (34.2)</td>
<td>332 (31.4)</td>
<td>332 (33.4)</td>
<td>340 (32.2)</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>
</tr>
<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 (38.1)</td>
<td>398 (37.7)</td>
<td>389 (39.2)</td>
<td>388 (36.7)</td>
</tr>
<tr>
<td>Use of heparin</td>
<td>708 (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>Packed 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport with catheter(s) in place</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)</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</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>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.

©2009 American Medical Association. All rights reserved.

(Reprinted) JAMA, March 25, 2009—Vol 301, No. 12 1237
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.33

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

<table>
<thead>
<tr>
<th>No. of catheters at risk</th>
<th>Duration of Catheter Maintenance, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3 Days</td>
</tr>
<tr>
<td>1762 1378 949 678 482 325 228 156</td>
<td></td>
</tr>
<tr>
<td>CHGIS</td>
<td>7 Days</td>
</tr>
<tr>
<td>1908 1524 1070 750 538 386 272 200</td>
<td></td>
</tr>
</tbody>
</table>

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

| Variable                                    | Incidence, No./1000 Catheter-Days | ITT Analysis | Per-Protocol Analysis
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CHGIS (n = 1953)</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
</tbody>
</table>

| Catheter colonization >10 CFUs/plate        | 0.36 (0.28-0.46) | <.001 | 0.35 (0.27-0.45) | <.001 |
| Catheter-related bloodstream infection      | 0.24 (0.09-0.65) | .005 | 0.24 (0.09-0.63) | .004 |
| Major catheter-related infection            | 0.39 (0.16-0.93) | .38 | 0.38 (0.16-0.92) | .39 |

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). |

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.
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 case 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 CRI.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 soil- 
goals 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.

Author Affiliations: INSERM U823, University Joseph Fourier, Grenoble; Institute of Neuroscience, Grenoble; University Hospital, Grenoble, France; Dr Timsit, MS Calvino-Gunther, and Dr Francais; Medical Intensive Care Unit, Albert Michallon University Hospital, Grenoble, France (Dr Timsit and Schwebel and MS Calvino-Gunther); Medical Intensive Care Unit (Dr Boudouma), Surgical Intensive Care Unit (Dr Geoffroy), Bacteriology Department (Dr Armand-Lefevre), Drug Delivery Department (Dr Arnaud), and Infection Control (Dr Lucet). Bichat Claude Bernard University Hospital, Paris, France; Medical Surgical Intensive Care Unit (Dr Geoffroy) and Microbiology Department (Dr Benali), Saint Joseph Hospital Network, Paris, France; Surgical Intensive Care Unit (Dr Pease) and Microbiology Department (Dr Leflon), Beaujon University Hospital, Clichy, France; Surgical Intensive Care Unit (Dr Henri-Chapelin); Microbiology Department (Dr Delafontaine and Croze), Grenoble University Hospital, Grenoble, France; Medical Surgical Intensive Care Unit (Dr Haouache) and Microbiology Department (Dr Chaplain), Delafontaine Hospital, Saint Denis, France; Physiology Department, Cochin Hospital, Paris, France (Dr Adrie); Micro-Biology and Hygiene, Necker Hospital, Paris, France (Dr Zahar); National Biomedical Agency, Saint Denis la Plaine, France (Dr Thuong); and Assistance-Publique Hôpitaux de Paris and University Paris VII Denis Diderot, Paris, France (Dr Lucet).

Author Contributions: Dr Timsit had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Timsit, Schwebel, Lucet.

Acquisition of data: Timsit, Schwebel, Boudouma, Geoffroy, Garrouste-Orgeas, Pease, Herault, Haouache, Calvino-Gunther, Gestin, Armand-Lefevre, Chaplain, Ben-Djira, Croze.

Analysis and interpretation of data: Timsit, Schwebel, Leflon, Francais, Adrie, Zahar, Thuong, Arnaud, Lucet.

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

Critical revision of the manuscript for important intellectual content: Timsit, Schwebel, Boudouma, Geoffroy, Garrouste-Orgeas, Herault, Haouache, Gestin, Armand-Lefevre, Leflon, Chaplain, Ben-Djira, Francais, Adrie, Zahar, Thuong, Arnaud, Croze, Lucet.

Statistical analysis: Calvino-Gunther, Francais.

Obtained funding: Timsit.

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

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

Dr Boudouma and Boudouma contributed equally to the study.

Financial Disclosures: Dr Lucet reported receiving lecture fees from 3M Inc, manufacturer of the semipermeable transparant dressing, used in this study. No other authors reported disclosures.

Supporting Information: This study was supported by a public grant from the French Ministry of Health (Projet Hospitalier d’Innovation 2006–2008; PH 06-1910). 3M Inc donated the Biopatch dressings used in the study.

Role of the Sponsor: Neither the French Ministry of Health nor Ethicon Inc had any role in the design or conduct of the study; the management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Members of the Dressing Study Group (in alphabetical order): Invited (2006): Philippe B flown (Paris, Bichat Claude Bernard), Antonio Alvarez (Delafontaine Hospital), Clara Arai-Somohana (Grenoble), Cécile Aubron (Paris, Bichat–Claude Bernard), Didier Barnoud (Grenoble), Lucie Banka (Clichy, Beaujon), Abdel Benbara (Clichy, Beaujon, Agnes Bonadona (Grenoble), Claire Bonneville (Clichy, Beaujon), Regis Bronchard (Paris, Bichat–Claude Bernard), Christophe Broux (Grenoble), Jean Carlet (Paris, St Joseph), Cyrille de Vaumas (Paris, Bichat–Claude Bernard), Philippe Delcette (Grenoble), Gerardine Dessertane (Grenoble), Dominique Falcon (Grenoble, Lou Ferrera (Paris, Bichat–Claude Bernard), Claire Francony (Grenoble), Stephane Freneza (Grenoble), Stephanie Gascioli (Clichy, Beaujon), Mathieu Gna (Clichy, Beaujon), Rebecca Hamidifar-Roy (Grenoble), Laura Hamer (Grenoble), Hana Hamzaouzi (Clichy, Beaujon), Jerome Hanna (Grenoble), Claude Jacquot (Grenoble), Nathalie Kermarek (Paris, Bichat–Claude Bernard), Karim Kahlhi (Clichy, Beaujon), Sigismond Lasocki (Paris, Bichat–Claude Bernard), Pierre La-vagne (Grenoble), Yves Leport (Paris, Bichat–Claude Bernard), Benoit Misset (Paris, St Joseph), Philippe Montravers (Paris, Bichat–Claude Bernard), Bruno Mouvillier (Paris, Bichat–Claude Bernard), Catherine Paugam (Clichy, Beaujon), Francois Philippard (Paris, St Joseph), Aymery RestouX (Clichy, Beaujon), Alexis Tabah (Grenoble), Pierre Trouiller (Clichy, Beaujon), Vincent Wellmann and Zoltan Wolff (Paris, Bichat–Claude Bernard). Study monitors, research nurses, and biobehavioural techniciens: Caroline Brouse, Silvia Calvina, Monia Fahim, Floraine Goyer, Nadira Khour, Daniel Menuet, Sylvie Verne, Karima Sehil.


Statistical Analysis: The methods and full statistical analysis were performed in the INSERM U823 unit (Institut National pour la Santé et la Recherche Médicale) by Adrien Francais and Aurélien Vesin under the supervision of Valérie Siroux and Jean-François Timsit.

REFERENCES


©2009 American Medical Association. All rights reserved.


