

A Novel Integrated Chlorhexidine-impregnated Transparent Dressing for Prevention of Vascular Catheter-related Bloodstream Infection: A Prospective Comparative Study In Healthy Volunteers

Dennis G Maki, MD¹, Julie Stahl, BS², Cassie Jacobson, MS², Janine Pyrek, MS³

¹ Section of Infectious Diseases, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI;

² Medical Materials Laboratory, 3M Corporation, St Paul MN; ³ P-Value Statistical Consulting, Moab, UT

ABSTRACT

Background: Most catheter-related bloodstream infections caused by short-term noncuffed central venous and arterial catheters derive from cutaneous microorganisms colonizing the insertion site. Technologic innovations to continuously suppress the cutaneous microflora about the catheter can materially reduce the risk of catheter-related BSI.

Objective: To better understand potential efficacy for prevention of catheter-related bloodstream infection with noncuffed vascular catheters and subjects' tolerance of two chlorhexidine gluconate (CHG)-impregnated catheter site dressings, a CHG-impregnated sponge dressing (Biopatch™, Johnson and Johnson), designed to be affixed about the catheter, then immobilized with a nonmedicated polyurethane dressing, and a novel integrated CHG-impregnated transparent polyurethane dressing (Tegaderm™ CHG, 3M).

Design: Measurement of immediate surface antimicrobial activity (quantitative kill over 15 minutes) of the new integrated CHG dressing and a nonmedicated polyurethane dressing (control) against 15 clinical isolates representing 9 species, and two open-label *in vivo* trials in healthy volunteers of immediate and long term cutaneous antimicrobial activity, one analyzing prevention of skin floral regrowth on alcohol prepped subclavian sites and the other, cumulative kill of skin flora on unprepped sites over 10 days of exposure.

Setting: Medical Division Laboratories of 3M Company and Hill Top Research, Inc., Miami, OH.

Participants: Forty-eight healthy adults without primary skin dis-

ease or known allergy to CHG participated in the regrowth study on prepped subclavian sites and 29 subjects participated in the trial assessing kill of normal flora on unprepped skin.

Results: The new integrated CHG transparent dressing provided excellent *in vitro* kill when microorganisms were applied to the CHG surface of the dressing. In the regrowth trial, at day 7, the new integrated CHG transparent dressing showed significantly lower regrowth post prep compared to the control ($P < 0.0001$). At day 10, both CHG dressings showed significantly lower regrowth ($P < 0.0003$). There was a statistically significant difference between the new integrated CHG-impregnated transparent dressing and the CHG-impregnated sponge dressing at day 7 ($\Delta \log_{10}$ CFU 0.80, $p \leq 0.02$). In the unprepped study, the new dressing showed significantly higher log reductions at day 1 and day 4 (day 1 $\Delta \log_{10}$ CFU/cm² 0.60 and day 4 $\Delta \log_{10}$ 0.80) ($P \leq 0.03$; $P \leq 0.0008$). All three dressings were well tolerated, with none producing hypersensitivity.

Conclusions: Both CHG dressings provided excellent long-term surface antimicrobial activity against diverse microbial species and cutaneous floral suppression, and were well tolerated. The new integrated transparent CHG-impregnated dressing provided superior prevention of floral regrowth on prepped sites and progressive kill of the cutaneous microflora on unprepped sites. The new integrated transparent CHG-impregnated dressing is easier to apply, reliably secures the catheter, permits continuous inspection of the insertion site, obviates the need for every-other-day site care and warrants evaluation in a prospective randomized clinical trial.

INTRODUCTION

Short-term non-cuffed and non-tunneled central venous and arterial catheters are widely used inpatient care. The most frequent life-threatening complication of vascular access is catheter-related bloodstream infection (CRBSI), which is associated with significant morbidity, prolongation of hospitalization, excess healthcare costs and attributable mortality.^{1,2} Most CRBSIs with short-term catheters are caused by cutaneous microorganisms from the insertion site.³⁻⁵ The use of chlorhexidine gluconate (CHG) for cutaneous antisepsis prior to catheter insertion provides substantial protection against CRBSI,^{6,7} however, the microflora can rapidly grow back and invade the catheter tract and cause infection.³⁻⁶

A novel CHG-impregnated hydrophilic vascular access site dressing has been developed which can be affixed to the skin about a

percutaneous catheter at the time it is inserted (Biopatch™, Johnson and Johnson, Dallas, TX); the dressing maintains a high concentration of CHG on the underlying skin surface,¹¹ and clinical trials have shown the dressing provides significant protection against colonization of catheters and CRBSI.⁸⁻¹⁰

A new integrated transparent CHG-impregnated vascular access site dressing has been developed (Tegaderm™ CHG, 3M, St Paul, MN) which is easier to apply, reliably secures the catheter and permits continuous inspection of the insertion site. We report comparative analyses of the two novel CHG-impregnated dressings in healthy volunteers to measure relative bactericidal surface activity at the site for prevention of CRBSI and subjects' tolerance of the dressings.

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Features of the two CHG-impregnated Dressings

The established CHG dressing studied (Biopatch™) is a hydrophilic polyurethane semipermeable absorptive foam disc 1 inch in diameter with a central hole and radial slit (Figure 1), impregnated with 86.5 mcg of chlorhexidine gluconate per mg dry weight. The dressing is conformable, highly permeable to water vapor, and can absorb up to eight times its weight in fluid; chlorhexidine incorporated into the dressing is released onto the skin surface beneath the dressing at a controlled rate for at least 7 days.¹¹ The dressing is designed to be affixed to the skin surface around a percutaneous vascular catheter, then immobilized and covered with a sterile nonmedicated polyurethane dressing, to inhibit microbial growth on the site and prevent invasive infection of the catheter tract.

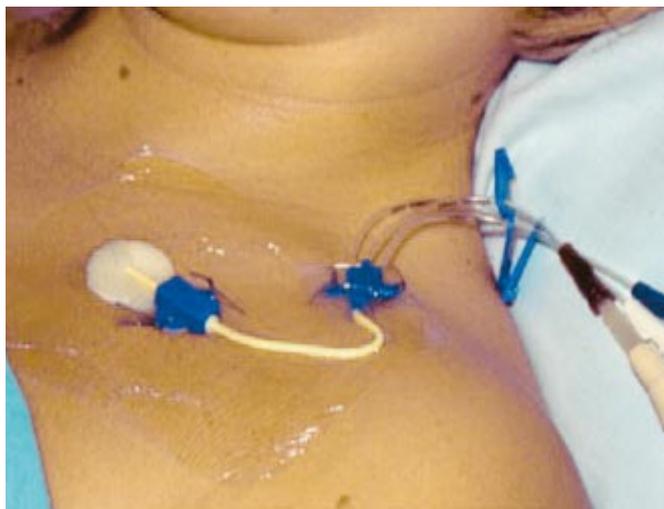


FIGURE 1. The chlorhexidine-impregnated sponge dressing.

The new integrated CHG-impregnated transparent dressing (Tegaderm™ CHG, 3M) obviates the need for a 2-step application: a water vapor-permeable CHG-impregnated gelpad is incorporated onto the adhesive side of a transparent polyurethane dressing, and the CHG-impregnated gelpad is applied directly over the insertion site at the time of catheter insertion or during follow up site care. The gel rapidly softens at skin temperatures and flows about the catheter, providing intimate contact of the CHG-impregnated surface with the entire insertion site (Figure 2). The gel also absorbs up to eight times its weight in fluid, preventing accumulation of moisture on the site. The integrated dressing tightly secures the catheter, preventing any pistoning movement that can facilitate entry of microorganisms into the insertion tract.¹

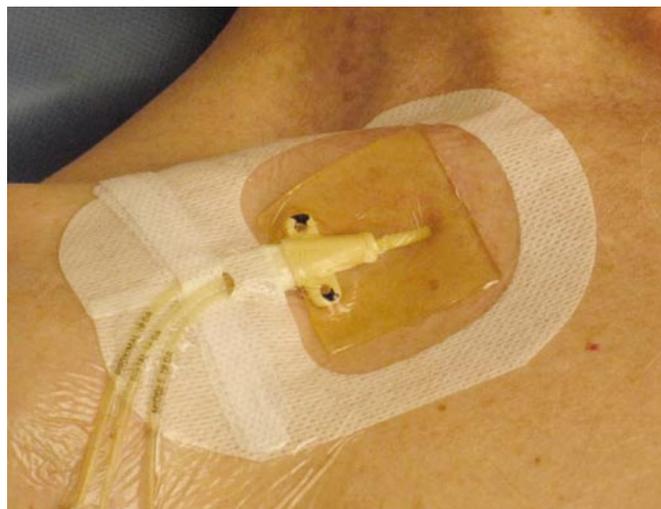


FIGURE 2. The novel integrated CHG-impregnated transparent dressing.

METHODS

In Vitro Time-kill Study

The bactericidal surface activity of the new integrated CHG-impregnated transparent dressing was tested against a panel of 15 microbial strains obtained from the ATCC collection: methicillin-sensitive *Staphylococcus aureus* (2 strains), methicillin-resistant *S aureus* (MRSA) *Staphylococcus epidermidis* (2 strains), *Micrococcus luteus*, *Enterococcus faecalis* (2 strains), vancomycin-resistant *Enterococcus faecium*, *Escherichia coli* (2 strains), *Serratia marcescens*, *Pseudomonas aeruginosa* (2 strains), and *Candida albicans*.

The adhesive side of a control nonmedicated polyurethane film dressing (Tegaderm™, 3M) and the gelpad surface of the new integrated CHG-impregnated transparent dressing were each inoculated with 50- μ L of a suspension containing 5×10^8 CFU/mL ± 0.5 log. Inoculated dressings were covered and incubated at 35 ± 2 °C then sampled in duplicate at 1, 3, 5, 10 and 15 minutes by immersing the entire dressing into 20 mL of PBS containing 0.04% KH_2PO_4 , 1.0% Na_2HPO_4 , 0.1% Triton X100 and the neutralizers, 0.9% lecithin, and 6.0% Tween 80 (pH 7.9), then vortexing for 2 minutes. The capacity of the neutralizers to immediately quench any carry-over CHG activity in the sampling solution was validated. Immediately after vortexing, ten-fold serial dilutions in phosphate-buffered water were plated in duplicate onto TSA (Difco, Detroit, MI) and plating within 20 minutes. The lower limit of detection for the culture method was 20 CFU/mL. After incubating overnight at 35 ± 2 °C, counts on duplicate plates were averaged and converted to \log_{10} CFU/mL, permitting measurement of a time kill curve.

Source of Subjects for *In Vivo* Trials

These studies were approved by an external IRB. Healthy adult volunteers not known to be allergic to CHG and without a primary skin disorder were informed of the nature of the study before written consent to participate was requested. Subjects were pre-screened for high baseline cutaneous bacterial counts (skin floral densities $\leq 2.5 \log_{10}$ CFU/cm²).

Subjects agreed not to participate in other studies and to refrain from using any systemic antimicrobials or cutaneous antiseptics 14 days prior to and during the study.

The Regrowth Study was conducted at HillTop Research in Miamiville, OH. Forty-eight subjects were enrolled, and 32 completed the study. Average age of subjects was 52 years (range 25-70), 51% were female and most (88%) were non-hispanic Caucasian; 12% were African-American. Average height was 67 inches, average weight 162 pounds, mean BMI 24.9.

The Unprepped Study was conducted in the Medical Division Laboratory of 3M Company in St Paul, MN. A total of 29 subjects were enrolled. Twenty subjects completed the 4 time points and 10 subjects completed all 5 time points.

The average age of subjects was 47 years (range 27-62), 55% were female and 97% non-hispanic Caucasian. The average height of the was 67 inches and average weight 183 pounds; the mean BMI was 28.3.

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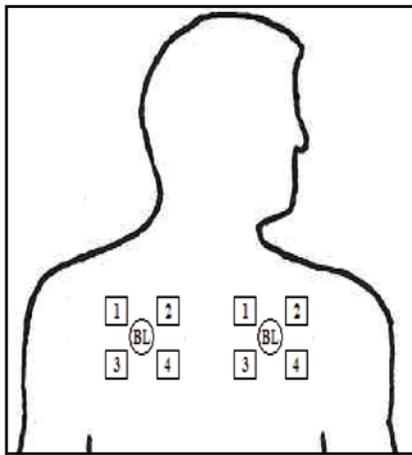


FIGURE 3. Site map for baseline cutaneous floral sampling and positioning of the three test dressings and post-prep sampling in the trial assessing suppression of regrowth on prepped subclavian sites.

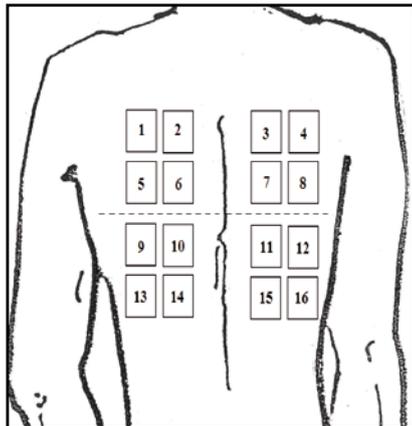


FIGURE 4. Site map for baseline floral sampling, positioning of the two test dressings and followup sampling at 5 timepoints in the trial of *in vivo* time kill of normal flora on unprepped skin.

Microbiological Methods for *In Vivo* Trials

The same microbiological sampling method was used in both of the comparative trials. Quantitative cultures were obtained using the Williamson-Kligman scrub cup technique, designated by the FDA as the technique of choice for skin floral sampling. The sampling solution consisted of 75mM PBW, containing 0.1% Triton X100, 3.0% Tween 80 and 0.3% Lecithin adjusted to pH 7.9±0.1.

A sterile scrub cup (2.54 cm) is placed on the sampling site and apposed to the skin surface. A 2.5-mL volume of a sampling solution (containing neutralizers) is pipetted into the cup and the area scrubbed with moderate pressure for 1 minute using a sterile policeman, following which the solution is withdrawn and placed in a sterile test tube; the process is repeated with an additional 2.5-mL of sampling solution and the two samples are pooled. Serial ten-fold dilutions in PBW are plated in duplicate onto TSA and incubated for 72 hours at 35 °C; colonies were enumerated and converted to mean log₁₀ CFU/mL.

In Vivo Trials in Volunteers

Two open-label *in vivo* comparative trials were conducted in healthy volunteers to assess the immediate and long term surface cutaneous antimicrobial activity of the two CHG (Tegaderm™ CHG and Biopatch™) dressings and a control nonmedicated transparent dressing (Tegaderm™, 3M).

Study of Suppression of Regrowth on Prepped Subclavian Sites

This study was conducted in the volunteers to assess the capacity of the test dressings to suppress floral regrowth following cutaneous prepping for 1 minute with 70% isopropyl alcohol. This was a within-subjects randomized design in which each subject served as his or her own control by using five test sites over each subclavian vein (Figure 3).

On study-day 0, two skin sites located in the center of the two subclavian test areas were sampled for baseline floral counts. One test area (right or left), using a randomization schedule, was prepped with 70% isopropyl alcohol for 1 minute. After the site air dried, an immediate post-prep skin flora sample was obtained and the three test dressings were applied following a randomization schedule; the CHG-impregnated sponge dressing was immobilized and covered with a nonmedicated transparent dressing (Tegaderm™, 3M). The dressings were left in place for 7 or 10 days. Quantitative skin cultures by the scrub cup technique were obtained from one side (by random assignment) after 7 days and the contralateral side after 10 days.

In Vivo Time Kill of Normal Flora on Unprepped Skin:

This study was conducted to assess the relative antimicrobial activity of two CHG dressings against normal cutaneous microflora on the back by measuring floral counts under the dressings after 1, 2, 4, 7 and 10 days on sites that were not prepped with an antiseptic at the outset. This also was a within-subjects randomized design in which each subject served as their own control by using multiple test sites over each side (Figure 4).

On study-day 0, two randomized skin sites on each of the two test areas (one on the right and the other on the left) were sampled for baseline counts. The two test CHG dressings were then randomly applied to the remaining sites. Again, the CHG-impregnated sponge dressing was immobilized and covered with a nonmedicated transparent dressing.

By random assignment, one of each test CHG dressings was removed from each side on study days 1, 2, 4, 7 and 10 and quantitative skin cultures were obtained, using the PBS sampling solution containing neutralizers.

Statistical Methods

The regrowth study on prepped subclavian sites was designed to detect a 0.5 log difference (Δ) in bacterial counts between the two CHG dressings tested, assuming a 0.9 log standard deviation and a 2-sided alpha of 0.05 and 80% power. The unprepped skin study was designed to detect a 0.75 log difference, assuming a 1.3 log standard deviation and a 2-sided alpha of 0.05 and 80% power. Bacterial counts were converted to log₁₀ CFU /cm² prior to analysis; counts <1 CFU /cm² were converted to a log₁₀ of zero. Two-tailed P-values <0.05 were considered significant.

For the regrowth study, the differences in mean log regrowth among the three treatment groups on subclavian sites were assessed using an ANOVA for randomized block designs. Significance was assessed at P≤0.05 (2-tailed). Pair-wise comparisons were tested using Tukey's test to hold the experiment-wise error ≤ 0.05. For the unprepped skin study, paired t-testing on the log reduction from baseline was used to compare the effects of treatment and calculated for each time point. Since these study utilized a paired design, if data from one of the two test CHG dressings were not available, data from the other treatment group on that day was not included in the analysis. However, to take missing data into account, we undertook two additional analyses, both using a likelihood-based repeated measures analysis (SAS's PROC GENMOD with the GEE approach). In the first approach all the non-missing data were used, regardless of availability of a treatment pair at a given time; this analysis used the observed data to model the missing data. In the second approach, missing values were replaced with the value from the previous non-missing day, the Last Observation Carried Forward (LOCF) technique.

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RESULTS

In Vitro Time-kill Study

The study showed minimal \log_{10} reductions (<0.28 log) of any of the test strains on the nonmedicated control dressing, whereas \log_{10} reductions ranged from 3.22 to 6.30 for the new integrated CHG-impregnated transparent dressing after 15 minutes of exposure for 12 of the 15 strains. Lesser reductions were seen with *E. faecalis* ATCC 29212 (2.18 log), *E. faecium* (VRE) ATCC 51559 (2.93 log) and *M. luteus* ATCC 7468 (0.22 log).

Study of Suppression of Regrowth on Prepped Subclavian Sites

At day 7, the new integrated CHG transparent dressing showed significantly lower regrowth post prep compared to the control ($P<0.0001$). At day 10, both CHG dressings showed significantly lower regrowth ($P<0.0003$). (Figure 5) There was a statistically significant difference between the new integrated CHG-impregnated transparent dressing and the CHG-impregnated sponge dressing at day 7 ($\Delta \log_{10}$ CFU 0.80, $p<0.02$).

There were no serious adverse events in the study, and all 3 dressings were well tolerated.

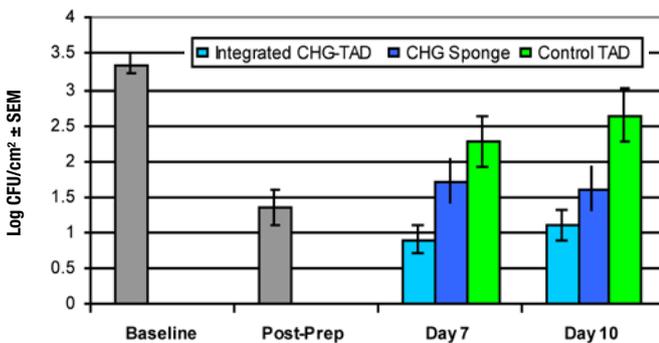


FIGURE 5. Suppression of regrowth on prepped subclavian sites with the two CHG-impregnated dressings in healthy volunteers.

At day 7, the new integrated CHG transparent dressing showed significantly lower regrowth post prep compared to the control ($p<0.0001$). At day 10, both CHG dressings showed significantly lower regrowth ($p<0.0003$). There was a statistically significant difference between the new integrated CHG-impregnated transparent dressing and the CHG-impregnated sponge dressing at day 7 ($\Delta \log_{10}$ CFU 0.80, $P<0.02$).

In Vivo Time Kill Of Flora On Unprepped Skin

A plot of the \log_{10} counts for the 20 subjects with paired data available at day 7 is provided in Figure 6. In comparing bacterial log reductions from baseline over time, the new integrated CHG-impregnated transparent dressing had directionally higher average log reductions compared to the CHG-impregnated sponge-disc dressing at each day, however, these differences only achieved statistical significance at day 1 and day 4 (day 1 $\Delta \log_{10}$ CFU/cm² 0.60, and day 4 Δ 0.80) ($P=0.03$; $P=0.0008$). The likelihood-based repeated measures analysis, which included both dressing and time in the model, showed the new integrated CHG-impregnated transparent dressing to be significantly more effective than the CHG-impregnated sponge dressing in reducing floral counts on unprepped skin across all time points ($P=0.008$); the result held whether the analysis was conducted on the available data only or on the data set where missing values were imputed using the non-missing values from a previous day by LCOF.

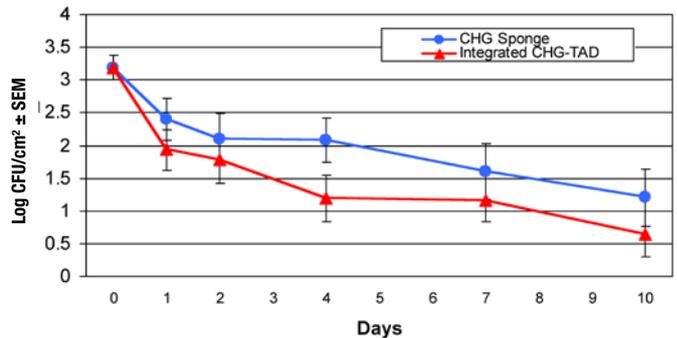


FIGURE 6. *In Vivo* time kill of normal flora on unprepped skin with the two CHG-impregnated dressings in healthy volunteers.

The likelihood-based repeated measures analysis, which included both dressing and time in the model, showed the new integrated CHG-impregnated transparent dressing to be significantly more effective than the CHG-impregnated sponge dressing in reducing floral counts on unprepped skin across all time points ($P=0.008$).

DISCUSSION

CHG has been used widely throughout the world for more than 50 years for cutaneous disinfection, hand hygiene and oral hygiene, and the safety of CHG is well established.¹² Clinically relevant high-level bacterial resistance has been very rare.¹³⁻¹⁵

The Biopatch™ hydrophilic CHG catheter site dressing has been a technologic advance for prevention of CRBSI with short-term vascular catheters. Recent prospective randomized trials of the dressing have shown major reductions in catheter colonization and CRBSI,⁸⁻¹⁰ but it is essential to apply the dressing properly if it is to be effective, with the CHG-impregnated side apposed firmly to the skin surface and the entire 360° circumference of the catheter protected, immobilized with a transparent polyurethane dressing (Figure 1). The dressing must not be simply laid on top of

the catheter at the insertion site, which commonly occurs in clinical practice and greatly diminishes its efficacy.

In this study, the new integrated CHG dressing showed powerful bactericidal activity against diverse nosocomial microbial species, and both CHG dressings studied showed excellent immediate and, especially, long-term cutaneous floral suppression and were well tolerated. The new integrated transparent CHG-impregnated dressing is easier to apply and less vulnerable to improper application, reliably secures the catheter, permits continuous inspection of the insertion site, and obviates the need for every-other-day site care. It now warrants evaluation in a prospective randomized clinical trial to determine if it also can prevent catheter colonization and reduce the incidence of CRBSI.



Dennis G. Maki, MD
dgmaki@medicine.wisc.edu
University of Wisconsin School
of Medicine and Public Health

600 Highland Ave. H4/572 CSC
Madison, WI 53792
608/263-1545

DISCLOSURE. Dr Maki holds no personal financial interest in the CHG dressings studied and has received no compensation for his participation in these studies.