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# Nasal photodisinfection and chlorhexidine wipes decrease surgical site infections: a historical control study and propensity analysis

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SUMMARY

***Background:*** Pre-operative decolonization therapy (DcTx) using chlorhexidine (CHG) body washes and/or intranasal mupirocin can reduce surgical site infections (SSIs), but compliance is often suboptimal.

***Aim:*** To assess the effectiveness of immediate DcTx using a novel approach of intranasal antimicrobial photodisinfection therapy (PDT) combined with CHG body wipes for the reduction of SSIs.

***Methods:*** Between 1st September 2011 and 31st August 2012, 3068 elective cardiac, orthopaedic, spinal, vascular, thoracic and neurosurgical patients were treated with CHG in the 24 h preceding surgery, and received intranasal PDT in the pre-operative area. SSI surveillance methodology remained unchanged from previous years and patients were followed for one year. Results were compared with those for a four-year historical control group of 12,387 patients as well as those for a concurrent control group of 206 untreated patients.

***Findings:*** A significant reduction in the SSI rate was observed between treated patients and the historical control group [1.6% vs 2.7%, $P = 0.0004$, odds ratio (OR) 1.73, 95% confidence interval (CI) 1.2815–2.3453]. This significant reduction was maintained on intent-to-treat analysis ($P = 0.021$, OR 1.37, 95% CI 1.9476–1.7854). Overall compliance with DcTx was 94%. A 1:4 propensity score analysis of matched treated and untreated patients demonstrated that DcTx reduced the risk of SSIs significantly ($P = 0.00026$, $z = 3.65$).

***Conclusion:*** The combination of CHG wipes and PDT immediately before surgery reduced SSIs, achieved excellent compliance, and was easily integrated into the pre-operative routine.



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## Introduction

Surgical site infections (SSIs) are among the most common healthcare-associated infections, with substantial morbidity and mortality.[1] The Institute for Healthcare Improvement estimates the additional length of hospital stay to be 7.5 days, with associated costs of $130–856 million/year.[2] Evidence supports decolonization therapy (DcTx) using peri-operative skin antisepsis and/or nasal decolonization with topical mupirocin ointment in an effort to reduce SSIs.[3–5] Unfortunately, compliance with decolonization is often suboptimal.[6]

The availability of prepackaged CHG body wipes for skin antisepsis has facilitated compliance with skin decolonization.[7] Intranasal photodisinfection therapy (PDT) is a promising complementary antimicrobial strategy that uses light energy to activate a photoactive methylene blue dye applied to the anterior nares.[8] It has been used safely and effectively on oral mucosa for the treatment of periodontal infections.[9] The combination of CHG body wipes and intranasal PDT has the theoretical advantage of broad-spectrum antimicrobial efficacy, rapid action, improved compliance, and low risk for development of antibiotic resistance. This paper describes a one-year quality improvement initiative to evaluate the effect on SSIs of using immediate pre-operative DcTx with intranasal PDT and CHG-impregnated wipes in selected non-general surgical populations, specifically elective cardiac, spinal, orthopaedic, thoracic, vascular and neurosurgical patients.

## Methods

### *Study hospital and SSI surveillance programme*

Vancouver General Hospital is a 728-bed adult tertiary care facility providing specialty complex surgical care. Procedures performed include coronary artery bypass grafting (with and without valve replacement), hip and knee replacements, craniotomies, ventriculo-peritoneal shunts, spinal procedures (with or without instrumentation/implants), thoracotomies and vascular grafts.[10] The SSI definitions of the Centers for Disease Control and Prevention National Healthcare Surveillance Network are used.[11] Cases are identified through routine surveillance using laboratory data, review of the surgical case list, voluntary surgeon reporting, daily ward reviews, reports from other facilities, and review of hospital re-admissions with a diagnosis of infection; this methodology has been consistent over the last 10 years and throughout the study period.[10]

### *Study design*

From 1st September 2011 to 31st August 2012, patients undergoing cardiac, orthopaedic, spinal, vascular, neurosurgical or thoracic procedures were offered immediate DcTx using CHG-impregnated wipes (Sage Products Inc., Cary, IL, USA) in the 24 h preceding surgery, and intranasal PDT (Ondine Biomedical Inc., Vancouver, Canada) in the pre-operative patient holding area. Patients were provided information on the decolonization programme in the pre-admission clinic or surgeon's office. Licensed practical nurses (LPNs) collected patient information and administered PDT from 0700 h to 1600 h on weekdays and from 0700 h to 1200 h at weekends. The PDT component of DcTx included applying a photosensitizer dye (0.1% methylene blue solution) to the anterior nares for 30 s and two 2-min cycles of illumination with a non-thermal red light with wavelength of 665 nm (Figure 1). Nasal cultures were performed prior to and after PDT therapy; the methods are described below. The study was approved by the ethics committees of Vancouver General Hospital and the University of British Columbia as a quality improvement project.

### *Data management*

The target population was patients undergoing elective clean surgical procedures, normally followed for development of an SSI as part of the infection prevention and control surveillance programme: cardiac, orthopaedic, spinal, vascular, thoracic and neurosurgical patients. Standardized daily data collected by LPNs included demographic information, American Society of Anesthesiologists (ASA) score, type of surgical procedure, surgeon, DcTx completion, compliance, reasons for non-compliance, adverse events and admission status; data were collected even if DcTx was not completed. Data were entered into an Access (Microsoft Corp., Seattle, WA, USA) database which was then exported to the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY, USA) for analysis. Cases that were not routinely followed for SSI surveillance were excluded from the analysis. Cases identified as SSIs by infection preventionists (functioning independently from the project) were entered into a separate Access database as per normal surveillance practice. SSIs were categorized as superficial or deep, and only one SSI per patient was counted. Patients were followed for one year from the time of surgery.

### *Statistical analysis*

The primary outcome was the effect of DcTx on SSI rates. The selected specialty services perform 7500 procedures/year, and an estimated 3300 patients are followed as part of routine SSI surveillance yearly. It was the intent to treat all of the patients routinely followed for SSI surveillance. The intervention group was defined as: (a) treated patients (i.e. patients receiving both CHG and PDT during the study period) and (b) untreated patients (i.e. patients who, unintentionally, did not receive PDT and/or CHG therapy during the study period). SSI rates of treated patients were compared with a historical control group of 12,387 patients. An intent-to-treat analysis was also performed using total SSIs in the treated and untreated patients compared with the historical controls. The literature supports a 30–40% reduction in SSIs with a 'horizontal' (i.e. directed against all potential pathogens) approach.[12] Comparing against a four-year average historical SSI rate of 2.7%, if the programme was expected to reduce SSIs by 35% (to 0.0175), a sample size of 2054 patients was required for an 80% chance to detect a significant difference with an alpha value of 0.05.

Treated patients were also compared with untreated patients using propensity score matching to attenuate potential confounding variables. A 1:4 rather than a 1:1 match was performed given the large imbalance in the numbers between the two groups. Covariates were selected consistent with risk adjustment strategies recommended by the National Hospital Surveillance Network.[11] All cases followed were categorized as clean elective procedures, and the vast majority received general anaesthesia. The additional factors used in matching included age, sex, procedure type, ASA score, total and median surgical

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**Figure 1.** Intranasal photodisinfection therapy. Prepackaged methylene blue (A) is applied to the nares for 30 s (B), followed by placement of the disposable nasal inserts (C) coupled to a 665-nm non-thermal diode laser that illuminates the nares for two, 2-min cycles (D).

time, t-time (75$^{th}$ percentile of the distribution of procedure duration from initial surgical incision to closure), procedures taking longer than 2 h, scheduled cases and cancer diagnosis. Matching was performed using Matchit Version 2.4-20 (http://r.iq.harvard.edu/docs/matchit/2.4-20/), with the nearest neighbour method and a caliper width of 0.2. A standardized difference of less than 0.1 was used, and this is accepted in the literature to indicate a negligible difference in the mean or prevalence of the covariate between the two groups (i.e. the means and prevalence rates of continuous and dichotomous variables were very similar between groups in the matched sample).[13,14] A conditional logistic regression model with treatment as the only covariate was performed on the matched data.

## *Microbiology*

Prior to and immediately following PDT, nasal swabs were collected using eSwabs (Copan Diagnostics, Murrieta, CA, USA), plated by the WASP automated plater (Copan Diagnostics, Murrieta, CA, USA) on to *Staphylococcus aureus* selective

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**Table I**
Surgical site infections (SSIs): treated patients vs historical controls

| Specialty | Treated patients | | Four-year historical control group | | *P*-values | OR |
|---|---|---|---|---|---|---|
| | SSIs | SSI proportion | SSI (average) | SSI proportion | | |
| Cardiovascular[a] | 19/628 | 0.030 | 83/3334 (21) | 0.025 | 0.44 | 0.82 |
| Neurological[b] | 2/502 | 0.004 | 31/2152 (7.75) | 0.014 | 0.076 | 3.65 |
| Orthopaedic[a] (all) | 6/892 | 0.007 | 50/2844 (12.5) | 0.018 | 0.025 | 2.64 |
| Spine | 18/475 | 0.038 | 136/1606 (34) | 0.085 | 0.0009 | 2.35 |
| Thoracic | 1/431 | 0.002 | 14/1357 (3.5) | 0.010 | 0.15 | 4.48 |
| Vascular | 3/140 | 0.021 | 25/1094 (6.25) | 0.023 | 0.92 | 1.07 |
| Total | 49/3068 | 0.016 | 339/12,387 (85) | 0.027 | 0.0004 | 1.73 |

OR, odds ratio.
[a] Variable use of chlorhexidine/mupirocin historically.
[b] Routine chlorhexidine shampoo and baths historically.

plates (BioRad, Montreal, Canada) and incubated at 35°C. Growth overnight was graded semiquantitatively as either heavy, medium, scant or no growth as per standard microbiological assessment protocols. Plates with no growth at 24 h were re-incubated and read at 48 h. Microbiological efficacy was determined by comparing post-PDT culture growth with pre-PDT culture growth; successful bioburden reduction was defined as reducing growth by one or more semiquantitative categories. Results were analysed for bioburden reduction as well as complete eradication of *S. aureus*.[15]

### *Adverse events*

All patients treated with intranasal PDT were asked about any symptoms related to their nose or throat, and were examined for any adverse facial events after the procedure. Patients who were concerned about any symptoms were referred immediately to the otorhinolaryngology service for further evaluation.

## Results

In total, 6090 patients were available for microbiological analysis (including results from a six-week ramp-up phase in the project where only orthopaedic and cardiovascular patients were treated), and PDT was administered to 5691 patients. Pre-PDT colonization rates of paired data ($N = 5578$) for meticillin-sensitive *S. aureus* (MSSA) and meticillin-resistant *S. aureus* (MRSA) were 23.2% (1295/5578) and 1.0% (54/5578), respectively. PDT reduced semiquantitative colony counts successfully in 84% (1133/1349) of patients [83.9% (1086/1295) of patients colonized with MSSA and 87% (47/54) of patients colonized with MRSA ($P = 0.09$) immediately after PDT]. Of those remaining in hospital, more than half (52%) of the patients who had initial complete eradication of *S. aureus* remained completely culture-negative 48 h after PDT.

The LPNs treated 5176 patients during the one-year study period when all services were enrolled (i.e. excluding patients from the ramp-up phase). In total, 3274 cases were clean elective surgical procedures, normally followed as part of routine SSI surveillance. Of these, 3068 (94%) cases were treated and 206 (6%) cases were not treated. Reasons for inability to treat included nurses unavailable to administer treatment (54 cases, 26.2%), patient called early to the operating room (40 cases, 19.4%), technical reasons (e.g. equipment unavailable; 23 cases, 11.1%), patient sent directly from unit to the operating room (24 cases, 11.7%), patient refusal (10 cases, 4.9%), miscellaneous (12 cases, 5.8%) and no information available (43 cases, 20.9%).

A four-year historical comparison was selected as the time when surgical services at Vancouver General Hospital were stable, with no change in patient population or service delivery. The study period was compared with the previous four years, and was remarkably stable with little difference from year to year with regards to total number of cases, sex, average age, scheduled cases, inpatient admissions, duration of surgery and ASA score >3. The SSI rate was 1.6% in the DcTx group compared with 2.7% in the historical control group ($P = 0.0004$, OR 1.73, 95% CI 1.2815–2.3453) (Table I). An intent-to-treat analysis combining both treated (49 SSIs/3068) and untreated (17 SSIs/206, combined rate 2.0%) cases compared with historical controls (339 SSIs/12,387, rate 2.7%) also confirmed the effectiveness of DcTx ($P = 0.021$, OR 1.37, 95% CI 1.9476–1.7854). The greatest decreases in SSI rates were noted in orthopaedic and spinal patients. When compared with the four-year historical average of 85 SSIs/year, a 42% reduction in SSIs was realized, the majority which would have been deep/organ space infections.

To reduce the effects of confounding when analysing observational data, a 1:4 propensity score matching of treated and untreated patients was employed to assess the effect of treatment on outcomes in the intervention group (Table II). Conditional logistic regression analysis of the matched data confirmed that DcTx was protective ($P = 0.00026$, $z = 3.65$).

*S. aureus* was the cause of infection in 35.9% of historical cases compared with 30.6% of treated cases. *S. aureus* was the primary pathogen in 58.8% (10/17) of untreated cases and 30.6% (15/49) of treated cases ($P = 0.044$, OR 3.24, 95% CI 1.0345–10.1357). Infections in spinal patients were largely responsible for this difference (Table III); all seven untreated spinal cases who developed an SSI had *S. aureus* compared with 10/18 treated cases ($P = 0.057$, OR 18.53, 95% CI 0.9205–372.9946). Microbiological cultures were available pre-operatively and after PDT for the treated group alone. Of the 15 treated (decolonized) patients with SSIs who had *S. aureus* infection, 10 patients (four MRSA and six MSSA) did not show *S. aureus* on any pre- or postoperative nasal cultures. Three of the remaining five patients who had MSSA pre-operatively in their nares had complete eradication of *S. aureus* after PDT, while two patients did not reduce their microbial burden. Pre-operative antimicrobial prophylaxis protocols to prevent both MSSA and MRSA were in place during this time.

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**Table II**
Summary statistics obtained after 1:4 matching using nearest neighbour method

| | Treated | Untreated | Total | *P*-values | Standardized difference |
|---|---|---|---|---|---|
| Number of patients, *N* | 704 | 188 | 892 | | |
| Age (years), mean (±SD) | 59.6 (±1.2) | 59.3 (±2.5) | 59.6 (±1.1) | 0.832 | 0.15 |
| Sex (male), *N* (%) | 329 (46.7) | 92 (48.9) | 421 (47.2) | 0.622 | 0.04 |
| ASA score of 3–5, *N* (%) | 433 (61.5) | 118 (62.8) | 551 (61.8) | 0.917 | 0.02 |
| Scheduled case, *N* (%) | 623 (88.5) | 160 (85.1) | 783 (87.8) | 0.211 | 0.1 |
| Cancer suspected/proven, *N* (%) | 113 (16.1) | 32 (17) | 145 (16.3) | 0.379 | 0.14 |
| Surgical time (min), mean (±SD) | 152.1 (±8.3) | 149.2 (±17.8) | 151.5 (±7.6) | 0.771 | 0.21 |
| Median time (min) | 120 | 111 | 118 | | |
| Procedures taking >2 h, *N* (%) | 351 (49.9) | 87 (46.3) | 438 (49.1) | 0.412 | 0.07 |
| t-time: cases >75th percentile, *N* (%) | 141 (20) | 40 (21.3) | 181 (20.3) | 0.685 | 0.03 |
| Type of service, *N* (%) | | | | | |
| Cardiovascular | 136 (19.3) | 39 (20.7) | 175 (19.6) | 0.68 | 0.04 |
| Neurological | 117 (16.6) | 29 (15.4) | 146 (16.4) | 0.74 | 0.03 |
| Orthopaedic | 198 (28.1) | 52 (27.7) | 250 (28) | 0.927 | 0.01 |
| Spinal | 104 (14.8) | 25 (13.3) | 129 (14.5) | 0.726 | 0.04 |
| Thoracic | 123 (17.5) | 36 (19.1) | 159 (17.8) | 0.593 | 0.04 |
| Vascular | 26 (3.7) | 7 (3.7) | 33 (3.7) | 1 | 0 |
| Infected, *N* | 13 | 14 | 27 | Not applicable[a] | Not applicable[a] |

ASA, American Society of Anesthesiologists; SD, standard deviation.
Note: matching cases to controls and not controls to cases.
[a] Contigency tables with Fisher's exact test, while statistically significant, are not suitable for matched data. The results of a conditional logistic regression analysis with treatment as the only covariate is shown below.

| | coef | exp (coef) | SE (coef) | *z* | *P* |
|---|---|---|---|---|---|
| Photodisinfection therapy | 1.44 | 4.21 | 0.394 | 3.65 | 0.00026 |

Seven (0.12%) patients reported a mild, transient pharyngeal irritation. All symptoms resolved rapidly with no residual effects. Two patients were referred to the otorhinolaryngology service and no tissue reaction was observed on visual examination.

## Discussion

DcTx with topical CHG and intranasal mupirocin is recommended as a strategy to reduce SSIs.[16–18] Focusing efforts on high-risk clean procedures is suggested because of the acknowledged difficulties in ensuring outpatient compliance with decolonization protocols, and because of the potential for the development of mupirocin resistance.[6,17] The combination of CHG wipes and nasal PDT used in this intervention has the advantage of targeting a broader range of organisms without the risk of developing antimicrobial resistance, and the ability to decolonize the skin and nares just prior to surgery was expected to increase compliance.

CHG has been a recommended pre-operative antiseptic for many years.[18,19] CHG-impregnated wipes are user-friendly, have been demonstrated to be effective in reducing healthcare-acquired infections, and the no-rinse formulation has the advantage of longer residual effect on the skin.[7,18–20] Patients who reported that they had not used the wipes prior to surgery were provided with CHG wipes in the pre-operative waiting room and assisted as necessary. Incorporating PDT into the pre-operative work flow was straightforward; the procedure took 10 min, but did require training in operation of the illumination machine.

PDT has been employed in the treatment of malignances and has been recognized for its antimicrobial activity. Non-

**Table III**
Surgical site infections (SSIs) with *Staphylococcus aureus*: comparison between patients treated and not treated with photodisinfection

| Specialty | Treated | | Not treated | | *P*-values | OR |
|---|---|---|---|---|---|---|
| | No. of SSIs | *S. aureus* SSI cases, *N* (%) | No. of SSIs | *S. aureus* SSI cases (%), *N* (%) | | |
| Cardiovascular | 19 | 4 (21.1) | 2 | 2 (100.0) | 0.083 | 17.22 |
| Neurological | 2 | 1 (50.0) | 2 | 1 (50.0) | NS | NS |
| Orthopaedic | 6 | 2 (33.3) | 3 | 0 (0) | NS | NS |
| Spinal | 18 | 8 (44.4) | 7 | 7 (100.0) | 0.057 | 18.53 |
| Thoracic | 1 | 0 (0) | 0 | 0 (0) | NS | NS |
| Vascular | 3 | 0 (0) | 3 | 0 (0) | NS | NS |
| Total SSIs | 49 | 15 (30.6) | 17 | 10 (58.8) | 0.044 | 3.24 |

OR, odds ratio; NS, not significant.

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oncological applications include treatment of periodontal disease, sinusitis and wound infections, and the potential uses for PDT continue to evolve.[9,21,22] The principles of PDT are simple; exposure to non-thermal light energy results in excitation of the photo-active molecules and production of toxic oxygen radicals. The singlet oxygen and other reactive oxygen species react with the bacterial cell membrane, resulting in cell death without affecting human cells.[21,22] In this case, methylene blue was used as the photosensitizer dye, applied to the anterior nares. PDT is approved by Health Canada for the treatment of skin infections, and has been used safely to treat periodontal disease for over five years.[9] The effect of PDT on nasal carriage of *S. aureus* was assessed concurrently, and results for the first 2221 patients have been reported previously. In this preliminary cohort, pre-PDT colonization rates for MSSA and MRSA were found to be 24.4% (453/1855) and 0.9% (16/1855), respectively, with six cases (0.6%) positive for both. Partial or complete decolonization when comparing pre- and post-PDT microbiological data was 85%, confirming that the technology was effective in reducing staphylococcus bioburden in the anterior nares.[15]

Fifteen treated patients had *S. aureus* infections; of these, five (33%) patients were identified as MSSA carriers on their initial pre-operative nasal swabs. *S. aureus* was successfully eradicated from the nares of three patients after PDT, and the organism persisted in two patients. Unfortunately, clinical samples were not available to determine whether the pre-operative isolates were the same strain as that acquired postoperatively. Ten of the 15 treated patients did not show *S. aureus* on any pre- or postoperative nasal cultures, but subsequently developed SSIs with *S. aureus* as the primary pathogen. Four of these patients had MRSA, suggesting nosocomial acquisition. The other six patients may have acquired their infections from either endogenous nasal or skin flora or nosocomially. The fact that repeated nasal cultures were negative suggests one of the latter two routes of acquisition.

A randomized controlled trial was not possible for pragmatic reasons, so the DcTx group was compared with a large stable historical control group, similar to the majority of available literature on pre-operative decolonization (with mupirocin and CHG). Additionally, a propensity score analysis was performed between the treated and untreated patients to control for confounding variables inherent in observational studies. The project was limited in that the incremental benefit of CHG wipes compared with PDT was not possible; this is an acknowledged limitation in the literature on this topic.

The historical comparison showed a highly significant positive outcome in treated patients. The intent-to-treat analysis further confirmed that immediate DcTx reduced SSIs. Despite the limitations of historical comparison, it is considered that the large sample size, the diverse surgical services selected for intervention, the long period of follow-up in cases, the historically stable surgical population, and the fact that SSI surveillance continued unaltered from previous years lends strength to the findings.

While randomized controlled trials are the gold standard to estimate the effects of treatment on outcomes, propensity score matching of observational data is useful to attenuate the bias in estimation due to confounding when randomization is not possible.[13,14] All procedures followed for SSI surveillance at the study hospital are already categorized as clean elective cases. It was not possible to match patients for diabetes or obesity because of missing data fields. However, the use of 10 other covariates that could increase surgical risk ensured a robust analysis exceeding that of many other interventional investigations on this topic.[23] Use of 2 x 2 tables and ORs is not suitable for matched data in a propensity analysis. Using the more appropriate conditional regression model, untreated patients were at 3.65 times greater risk of an infection compared with treated patients.

The greatest reduction in SSIs occurred in orthopaedic, spinal and neurosurgical patients, consistent with the literature.[16,17] Particular note should be made of the fact that, in contrast to other studies, cardiovascular patients did not experience a decrease in SSI rates.[24–26] A potential explanation was that the variable historical use of mupirocin and CHG muted any possible benefit that might have been seen. However, the failure to reduce infections was more likely due to a cluster of temporally related deep sternotomy infections that occurred during the study period. This event was investigated, addressed and resolved. Subsequently, the cardiovascular rate declined to 1.9% over the last seven months. This fiscal year (April 2012–March 2013), the combined SSI rate for all the specialty services was 1.3%, confirming that the reduction in cases has, at a very minimum, been sustained.

Importantly, immediate DcTx ensured a very high degree of compliance (94% of patients) without interrupting normal workflow. Intranasal PDT took approximately 10 min compared with five to seven days with traditional mupirocin. In fact, the nurses were able to treat 1912 patients in addition to those targeted for intervention. The seven cases of transient pharyngeal irritation were possibly related to trickling of the dye into the back of the throat. There were no complaints of altered taste or smell related to nasal treatment.

The combination of nasal PDT and CHG wipes as a strategy to decrease SSIs was safe, effective, and provided a viable alternative to traditional outpatient DcTx for non-general surgical procedures. This new strategy should be evaluated further, particularly because of its rapid action, broad-spectrum activity, minimal risk of antimicrobial resistance, and high rate of compliance.

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**Conflict of interest statement**
None declared.

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