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EVALUATION OF PROTOCOL CHANGE IN BURN-CARE MANAGEMENT USING THE COX PROPORTIONAL HAZARDS MODEL WITH TIME-DEPENDENT COVARIATES

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SUMMARY

Survival analysis methods are valuable for detecting intervention effects because detailed information from patient records and sensitive outcome measures are used. The burn unit at a large university hospital replaced routine bathing with total body bathing using chlorhexidine gluconate for antimicrobial effect. A Cox proportional hazards model was used to analyse time from admission until either infection with *Staphylococcus aureus* or discharge for 155 patients, controlling for burn severity and two time-dependent covariates: days until first wound excision and days until first administration of prophylactic antibiotics. The risk of infection was 55 per cent higher in the historical control group, although not statistically significant. There was also some indication that early wound excision may be important as an infection-control measure for burn patients.

INTRODUCTION

While the decline in incidence of burns has been slight, burn-care management has improved survival rates in the United States.[1,2] The costs for burn patients are twice as high as care for other hospital patients and less than one-third of the costs are retrieved.[3,4]

Infection of the burn wound is a common complication resulting in extended hospital stays and in the death of severely burned patients.[5] Control of infection remains a prominent component of burn management.[6] Burn patients are highly susceptible to serious infection from wound colonization by micro-organisms in the immediate environment of contiguous skin and mucous membranes or from fomites in the hospital environment. Any of the broad spectrum of bacteria, yeast, and fungi can colonize and invade burn sites, endangering the recovery of a severely burned patient.[7]

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Specialized burn-care units consider nosocomial infections to be a major concern.[8] Medical care involving vascular and urinary catheters must often be used in infected burn sites, and careful procedures must be used to avoid introduction of micro-organisms into the deeper tissues.[9] Additional infection control measures for burn patients include specialized surgical wound-care management and medical modalities.[10,11] As a control measure, severe burn patients often undergo operating room procedures (excision) to remove wound eschar. Special efforts in hospital burn care units, such as patient bathing with antimicrobial agents, are mandated to prevent infection spread.

Because of the urgency required for treatment of severely burned patients, evaluation of alternative infection control measures are not easily conducted in burn units.[12] A cohort study utilizing a historical control group was conducted to evaluate a replacement agent for body bathing and its effects on wound colonization/infection. The study period extended from 1983 to 1985 and involved 162 patients who were admitted to the burn unit of a university hospital.

In mid-1984 a protocol change was introduced: an antimicrobial detergent with 4 per cent chlorhexidine gluconate was substituted for daily total body bathing with bar soap. This infection-control intervention was instituted in hopes of reducing micro-organisms that might lead to wound colonization/infection and to prevent colonization of the wound with micro-organisms from the environment.[13] It was expected that this change in body bathing procedure would have the greatest effects on the incidence of microbial infection originating from the skin, hair, and hospital environment (especially *Staphylococcus aureus*), rather than on infection caused by microbial residents of the gastrointestinal tract (enteric bacteria and yeast). This study was undertaken to compare the efficacy of normal skin and hair disinfection for two different topical bathing agents as deterrents to burn wound colonization and infection.

METHODS

In studies utilizing a historical control group, careful analysis is required to accurately gauge intervention effectiveness.[14] Sensitive analytic methods that fully utilize clinical and medical data are needed to assess the impact of the intervention on burn infection. In this study we used the number of days until infection or discharge from the hospital in addition to whether or not a patient had an *S. aureus* infection. We used multivariate models to investigate the effect of a change in body bathing agents on the number of days until infection while controlling for the effects of other covariates. Cox proportional hazards regression[15] is used to estimate and test the effect of this intervention while adjusting for covariates that change over the course of the study (time-dependent covariates). The use of time-dependent covariates in the Cox proportional hazards model permits a greater utilization of clinical data by modelling when (in the course of patient treatment) a patient's risk for infection changes as a result of the administration of treatment or therapy.

Two antimicrobial agents used for bathing patients were investigated. Initial surface decontamination with 10 percent povidone-iodine (Betadine*) followed with regular bathing with soap (Dial*) was used exclusively from January 1983 to June 1984 and was replaced by 4 percent chlorhexidine gluconate (Hibiclens*) from June 1984 to the end of study period in December 1985. Body cleansing was done according to prescribed procedures endorsed by the manufacturer.

Medical records of patients treated during 18-month study periods before and after the protocol change provided information on burn wound infections and other medical information.

* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

We systematically reviewed medical charts and microbiology laboratory records and abstracted data to compare the routine bath and chlorhexidine intervention groups. Information from chart reviews included demographic data, clinical findings with concomitant diseases noted, dates of administration of antimicrobial drugs. microbiological isolations (dates and duration), dates of operating room procedures (excision), details of burn etiology, severity and total body surface area burned. All burns could be categorized as either moderate or major using the American Burn Association categorization.[16]

Although this study focuses on one group of infectious bacteria, *S. aureus*, routine surveillance was maintained on five groups of micro-organisms. Burn wounds were cultured at least every three days by the semi-quantitative swab method,[17] with colony counts of $\geqslant 10^4$ being defined as suggestive of infection and $<10^4$ being considered to be wound colonization. The number of days from admission to the burn unit until the first culture indicating colonization or infection was recorded.

Statistical Analysis

The Cox proportional hazards model was used to analyse the time from admission until either infection with *S. aureus* or discharge for 155 patients, controlling for baseline characteristics and the time-dependent covariates of days until first wound excision and administration of prophylactic antibiotics. The procedure 2L of BMDP statistical programs[18] was used to adjust for time-dependent covariates.

Patients in the historical control group that received the routine bathing care were coded as Group = 1, while those in the chlorhexidine intervention group were coded as Group = 0. To adjust for differences in burn severity, a continuous covariate, the percentage of the total body surface area burned, was included in the Cox model.

We used time-dependent covariates to control for the timing of a patient's treatment that reduces the risk of infection by modelling the transition from one category (untreated at risk) to another category (treated with reduced risk) prior to the occurrence of infection. For prophylactic antibiotic treatment an indicator variable time-dependent covariate was used such that a patient not yet treated who was at a possibly higher risk for infection had their covariate set equal to 1 until first administration of prophylactic antibiotics (after treatment their covariate was set equal to 0). This coding scheme leads to interpreting a positive coefficient as a beneficial effect of the treatment. The time-dependent covariate for excision was coded in a similar manner such that a positive coefficient implies a beneficial effect of excision.

Analysis of categorical risk factors was conducted using the Mantel–Haenszel χ^2 test to investigate the degree of association between group and infection status. Medians were compared using the Wilcoxon rank sum test and median times-until-event data were investigated using product-limit survival curves[19] and two-tailed logrank tests. The Statistical Analysis System[20] software was used in this preliminary investigation.

RESULTS

Description of study population

Of the 163 patients admitted to the burn unit during the course of the study period, 155 charts were reviewed and used in analyses. Excluded from the study were two patients that transferred to other hospitals within seven days of admission and one patient in the burn unit for non-burn injuries. Charts were incomplete or unavailable for five patients. There were 71 patients in the historical control group who received the routine bathing care and there were 84 patients in the intervention group who received the chlorhexidine intervention.

Table I. Characteristics of hospitalized burn patients

	Control group (%)	Intervention group (%)	Total
Number	71	84	155
Median age	32	36	
Gender			
Male	55 (77)	66 (79)	121
Race			
White	62 (87)	74 (88)	136
Severity of burn			
TBSA*	20	17	
Major†	63 (89)	77 (92)	140
Burn site			
Head	33 (46)	37 (44)	70
Trunk	54 (75)	75 (89)	129
Buttocks	13 (18)	24 (15)	37
Upper leg	30 (42)	32 (8)	62
Lower leg	20 (28)	28 (33)	48
Respiratory tract	24 (33)	21 (25)	45
Type of burn			
Flame	52 (74)	64 (76)	116
Scald	12 (17)	7 (8)	19
Electric	4 (6)	7 (8)	11
Chemical	3 (4)	6 (7)	9
Patient care			
Length of hospital stay (median days)	27	21	
Number of patients with excision	37 (52)	62 (74)	99
Median excisions per patient	2	1	
Median units of blood transfused	7·5	6	
Antibiotic use			
Penicillin	5 (7)	6 (7)	11
Ampicillin	7 (10)	12 (14)	19
Nafcillin	7 (10)	19 (23)	26
Cephalothin	7 (10)	3 (4)	10
Cefazolin	19 (26)	35 (42)	54
Gentamicin	1 (1)	10 (12)	11

* Median percentage of total body surface area burned
† American Burn Association categorization

The distribution of burn patients by group, demographics, burn characteristics and patient care characteristics are shown in Table I. The groups did not differ substantially by median age, gender, or race. Actual or suspected inhalation injury occurred among 29 per cent of all burn patients, and the percentage of patients with this type of injury did not differ between the two groups (Mantel–Haenszel χ^2 p-value = 0·252).

The severity of the burn, as rated by percentage of total body surface area burned, was greater in the control group. However, the percentage of full-thickness burn did not differ substantially between the groups (data not shown). The percentage of burns classified as major did not differ between the two groups. The body site of burn was similar for both groups; however, burns of the trunk and upper extremities occurred more frequently among members of the chlorhexidine intervention group.

The median length of hospital stay was longer for patients in the routine bathing group, but this difference was not statistically significant (Wilcoxon test p-value = 0·308). The number of excisions of the wound per patient did not differ between the groups. The percentage of patients treated with systemic antibiotics did not differ between the groups for spectrum II or spectrum III drugs (data not shown). The percentage of patients treated with spectrum I antibiotics was greater among members of the chlorhexidine intervention group for three antibiotics (Table I).

Microbes colonizing or infecting the burn wound

The groups differed in overall colonization/infection rate by any one or combination of micro-organisms isolated from the wound. The chlorhexidine intervention group had fewer overall infections.

The Mantel–Haenszel χ^2 analysis by micro-organisms indicated that the groups differed with respect to colonization/infection in three of the five micro-organism clusters studied (Table II). *S. aureus*, *Enterococcus*, and *Candida* yeast infections occurred at a significantly lower rate in the chlorhexidine intervention group. There was no difference in wound colonization/infection by either *Pseudomonas aeruginosa* or the gram-negative enterics. The number of infections by *S. aureus* and *Candida* on the trunk area were substantially less among members of the chlorhexidine intervention group than among members of the control group.

***S. aureus* infection-free survival time**

There were 49 patients (22 in the intervention group and 27 in the control group) with *S. aureus* isolated from the burn site. The estimated product limit median days without *S. aureus* infection for the control group was 47 days (Figure 1). Based on a logrank test (p-value = 0·039), the chlorhexidine intervention group had significantly longer time until infection.

Since nafcillin and cefazolin are used as anti-staphylococcal agents,[21] the time until first use of these drugs (prior to a positive culture report) was investigated using product-limit survival analysis (Figure 2). The median number of days until first administration of these drugs was 31 days in the intervention group. Based on a logrank test (p-value = 0·012), the first administration of these drugs was significantly earlier in the chlorhexidine intervention group.

In order to determine whether a significant trend toward earlier excision of burn wounds occurred during the study period, a product-limit survival analysis for the number of days until first excision was investigated (Figure 3). The median number of days until first excision was 18 days for the control group and 10 days for the intervention group. Based on the logrank test (p-value = 0·004), the first excision was conducted earlier in the chlorhexidine intervention group.

Multivariate analysis using Cox proportional hazards models was done to assess group differences adjusted for the effect of burn severity and the confounding effects of earlier prophylactic antibiotic administration and earlier excision in the intervention group. The results of several different Cox regression models are presented in Table III. The coefficient for the intervention effect in the four variable model yields a hazard ratio [exp(0·4383) = 1·55] indicating that the risk of infection was 55 per cent higher in the historical control group, although not statistically significant. A comparison of the two and three variable models shows that controlling for the effect of earlier surgical wound excision tended to decrease the estimated effects of the chlorhexidine intervention. Controlling for the effect of antibiotic treatment had a negligible effect on the coefficient representing the chlorhexidine intervention.

Analysis controlling for days until excision as a time-dependent covariate indicated that this procedure may play an important role in wound care management. The model χ^2 for the three variable including excision was large and significant, while the three variable model including

Table II. Number of patients with infection of burn wound

Culture colonization/infection	Control group (%)	Intervention group (%)	Total	*P*-value
Any micro-organism	55 (76)	47 (56)	102	0·007
S. aureus	27 (38)	22 (26)	49	0·017
P. aeruginosa	23 (32)	23 (27)	46	0·533
Enterics	22 (31)	15 (18)	37	0·063
Enterococcus	26 (36)	14 (17)	40	0·006
Candida	24 (33)	9 (11)	33	0·001

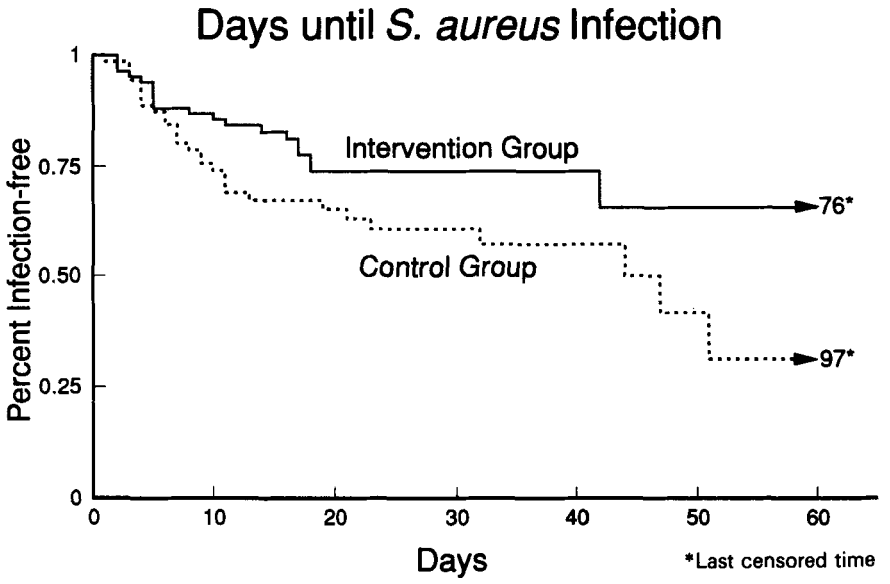

Figure 1. A comparison of *Staphylococcus aureus* infection-free status for the intervention and control groups of burn patients (logrank test p-value = 0·039)

antibiotic treatment had a smaller and non-significant model χ^2 value. The effect of pretreatment with anti-staphylococcal antibiotics was found to be non-significant and the coefficient became considerably smaller after controlling for the effects of surgical wound excision in the four variable model.

DISCUSSION

The primary goals related to choice of analytical method were to:

1. adjust for group confounders that may be present when using historical controls after a change in protocol,[22]
2. investigate a variety of possible risk factors for infection associated with treatment change while controlling for confounding factors in a multivariate analysis,[23] and

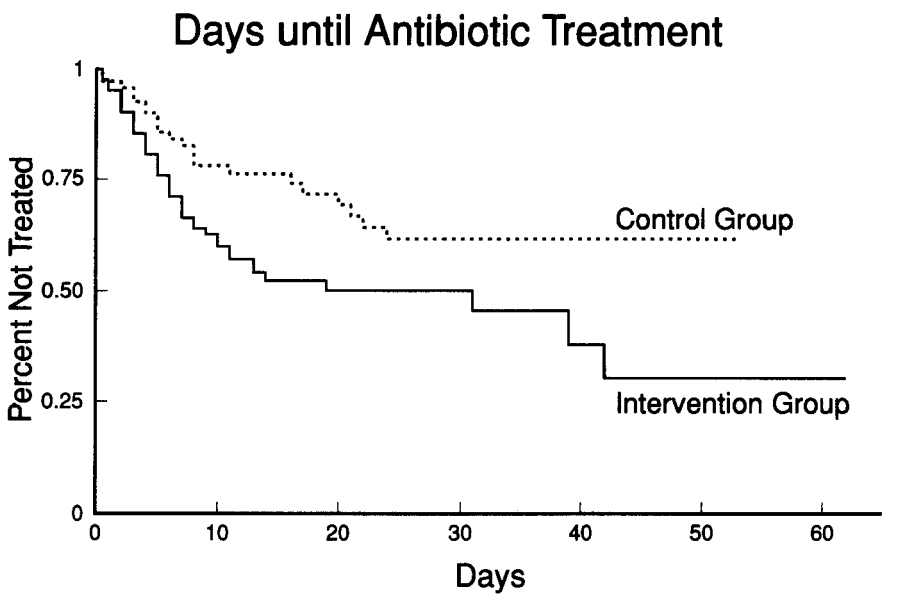

Figure 2. A comparison of time until prophylactic antibiotic treatment for the intervention and control groups of burn patients (logrank test p-value = 0·012)

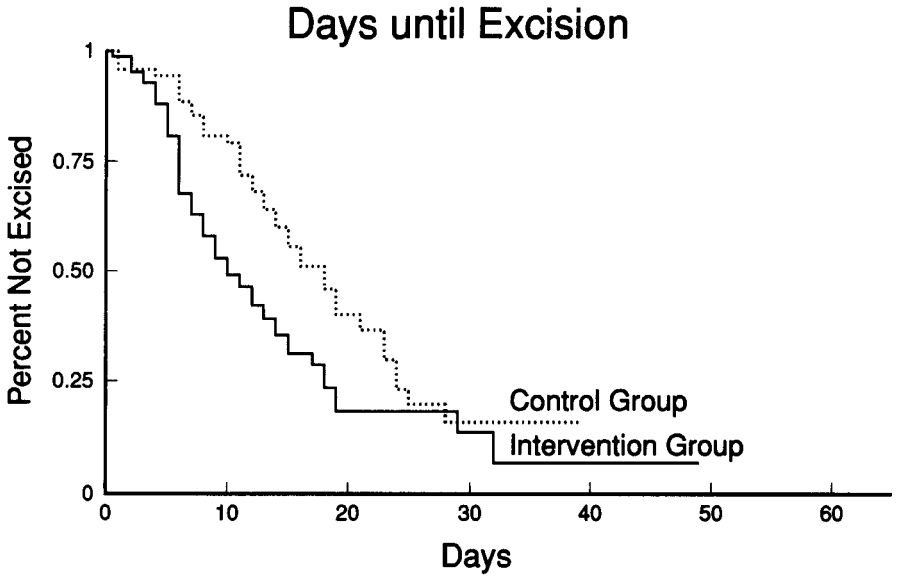

Figure 3. A comparison of time until excision for the intervention and control groups of burn patients (logrank test p-value = 0·004)

Table III. Cox regression analysis results

	Four variable model	Three variable models		Two variable model	One variable model
Model χ^2	8·41 (d.f. = 4)	8·41 (d.f. = 3)	5·62 (d.f. = 3)	5·51 (d.f. = 2)	4·19 (d.f. = 1)
p-value	0·078	0·038	0·132	0·064	0·041
Intervention*	0·4383	0·4439	0·5293	0·5446	0·5876
p-value	0·073	0·069	0·038	0·032	0·022
Per cent total body surface area burned	0·0075	0·0073	0·0083	0·0079	
p-value	0·292	0·296	0·242	0·259	
Days until excision†	0·7623	0·7676			
p-value	0·088	0·084			
Days until antibiotic treatment‡	0·0484		0·1130		
p-value	0·893		0·750		

* An indicator covariate coded 1 for the historical control (routine bathing care) group and coded 0 for the intervention (chlorhexidine bathing) group. *P*-values are based on a one-tailed test for the intervention effect, all other *p*-values are based on two-tailed tests

† A time dependent covariate coded as 1 before the surgical excision of burn wound and coded as 0 afterwards

‡ A time dependent covariate coded as 1 before the administration of prophylactic antibiotics and coded as 0 afterwards

3. employ time-until-event information[24] in the analysis to fully utilize the most sensitive measures available from patients' medical records.

The percentage of patients with colonization/infection of burn wounds was observed to decrease for three genera of micro-organisms after a protocol change involving the use of chlorhexidine gluconate as a total body bathing agent replacing routine hospital bathing.

Specifically, fewer patients had burn wounds infected with *S. aureus*, *Enterococcus*, and *Candida* after the change to chlorhexidine gluconate. In addition, lower concentrations of bacteria were recovered from the burn site of the patients receiving chlorhexidine gluconate body wash (data not shown).

Detailed analysis was done on the patients with *S. aureus* wound colonization. The product-limit survival analysis indicated that the intervention strategy was important in reducing burn infections. Drug regimens and wound care that may have been altered between the two groups were accounted for in analyses employing the proportional hazards model. When controlling for time until wound excision in a multivariate model the historical control group had higher risk of *S. aureus* infection although not statistically significant.

Because our study did not yield significant results for the intervention effect, we determined the number of *S. aureus* infected patients that would have to be observed in order to have an 80 per cent power to detect a hazard ratio of 1·55 with a significance level (alpha) of 0·05 based on a one-tailed test. The method described by Schoenfeld[25] yields a value of 129 *S. aureus* infected patients that would be required. Although this calculation does not adjust for the additional precision obtained by controlling for other covariates, more than the 49 infected patients observed in the 3 year data collection period of this study would be needed.

In patients with full-thickness burns, Kagan[26] found decreased risk of serious wound infections after early wound excision. In 1987 Heimback[27] concluded that early excision and grafting did decrease infectious wound complications for patients with burns between 20 per cent and 40 per cent of the total body surface area; however, he stated that more studies must be done in well-controlled settings.

In our study, the use of Cox regression was the only method that allowed for the control of the times until excision and antibiotic treatment before infection as confounders in establishing the relevance of procedural intervention in burn wound care and infection control. The major nursing staff and surgeons of the burn unit remained the same over the course of study, although a more aggressive approach to timely wound closure (earlier excision) was evident for the time period when chlorhexidine was used. Our application of time-dependent covariates allowed an assessment of the chlorhexidine intervention controlling for this change.

The chlorhexidine group did have significantly more burn injury on the trunk and upper extremities, and our multivariate analysis controlled for the percentage of the body surface area burned. However, the possibility exists that with more adequate, healthy, skin-graft-donor sites available (usually on the thigh), the excision and grafting might have been more successful for this group. There were no data available on actual wound healing time which might be used as a covariate in future studies to account for this difference. The chlorhexidine group did have slightly shorter hospital stays, possibly the result of the effectiveness of chlorhexidine in reducing the severity and number of infections.

We conclude that chlorhexidine gluconate may have beneficial qualities when used as a topical body cleansing agent for maintaining an infection-free hospital stay for burn patients, and that early excision may be an important procedure for infection control in burn-care management. Antibiotic treatment of the burn patient should be reserved for specifically documented infections; however, prophylactic systemic delivery of antibiotics has been widely practised without evidence of its beneficial qualities.[28] It is of interest that in this study, pretreatment with systemic antibiotics active against *S. aureus* did not show evidence of improving resistance to infection in the multivariate Cox model.

Unadjusted univariate analysis indicated a strong intervention effect and identified changes in the timing of the administration of prophylactic antibiotics and surgical wound excision. The magnitude and significance of the chlorhexidine intervention effect was diminished when analysed in a multivariate Cox regression model, carefully controlling for time-dependent covariates. We found some evidence of the importance of early wound excision as an infection-control measure for burn patients.

Studies such as this one are conducted in situations where a variety of factors are changing simultaneously. It remains difficult to attribute changes in outcome to any particular factor in clinical settings outside of a carefully conducted randomized clinical trial. Evaluation of the benefits of intervention strategies requires adjustment for any medical record data that may influence patient health. The careful application of multivariate statistical methods permits adjustment for those observed and recognized factors that influence patient outcome. This study showed the importance of controlling for time-dependent covariates when appraising the effectiveness of an intervention strategy.

We anticipate that a larger study which is currently in the planning stage will have more power to detect the effect of interventions on the infection-free status of hospital patients. Our study illustrates that the use of the most sensitive outcome measures and detailed information from patient records is essential for the evaluation of interventions and failure to use and correctly analyse this information may lead to false conclusions.

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