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PAPER

A Decade of Reduced Gram-negative Infections and Mortality Associated With Improved Isolation of Burned Patients

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Objective: To compare the incidence of gram-negative bacteremia (GNB) and mortality in patients with large burns (≥20% of total body surface) hospitalized in either an open ward (OW) or a single-bed isolation (IW) environment.

Design: Retrospective cohort study.

Setting: The US Army Institute of Surgical Research, Burn Center, Ft Sam Houston, Tex.

Patients: Two thousand five hundred nineteen consecutive patients with large burns divided into two 10-year cohorts. Patients in the first cohort period were treated under OW conditions; patients in the second cohort period, under IW conditions. Infection (bacteremia) data were from a laboratory database. A microbial surveillance system was used to monitor patient isolation. Mortality was compared with predicted mortality derived by logistic regression of outcome, burn size, and age of patients without bacteremia in the study.

Main Outcome Measures: Presence of GNB and survival.

Results: The incidence of GNB was higher in the OW cohort (31.2%) than the IW cohort (12.0%) ($P<.001$). The postinjury time of first GNB was delayed in the IW vs the OW cohort (28.9 days vs 11.8 days, respectively) ($P<.001$). For patients who had GNB in the OW cohort, mortality was higher than predicted (observed-predicted mortality ratio, 1.61) ($P<.001$). Such increased mortality was not present in the IW cohort. Multiple antibiotic-resistant gram-negative pathogens were endemic in the OW cohort. There was no evidence of cross infection or endemic conditions with multiple antibiotic-resistant gram-negative pathogens in the IW cohort.

Conclusion: Improvements in isolation of burned patients were associated with decreased incidence of GNB, delayed postinjury time of GNB, and improved survival. Improved survival is likely related to decreased susceptibility as a result of longer exposure to the benefits of treatment and wound closure. These results suggest that, in patients with severe burn injuries, gram-negative infections and the related mortality can largely be prevented.

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INFECTION IS a major cause of morbidity and mortality in hospitalized burned patients. We have previously estimated the added risk for mortality due to infection in a population of more than 5500 admissions for burns and demonstrated that bacteremia was associated with a 21% increase of mortality above that predicted by logistic regression analysis of injury severity and age.[1] When the bacteremic population was subdivided by pathogen, gram-negative opportunists were found to be the principal cause of the observed increase in mortality. Mortality in the group of patients with gram-negative bacteremia (GNB) was more than 50% greater than that predicted for patients without bacteremia.[1]

The clinical significance of gram-negative pathogens in burned patients became obvious after the introduction of newer generations of penicillin and aminoglycosides in the early 1960s.[2,3] *Pseudomonas aeruginosa* and members of the Enterobacteriaceae family became predominant and, during the subsequent 20 years, caused several endemics.[4,5] Distinguishing features of these endemics were multiple antimicrobial resistance and consistent biotypes within causative strains.

In 1983, the intensive care facilities of our burn center were modified so that seriously burned patients could be cared for in individual rooms rather than the previ-

See Methods on next page

From the US Army Institute of Surgical Research, Ft Sam Houston, Tex.

METHODS

In the present study, we have selected a 20-year period that includes the decades prior and subsequent to the opening of the new single-bed intensive care unit. We have arbitrarily used a total burn size of 20% or larger of the body surface as the inclusion criterion in an attempt to compare patients with serious injuries. Burned patients selected by this criterion represent more than 90% of those with bacteremia and 95% of those who died during the 20-year period. A comparison of patient demographics between the open-ward (1974 to 1983) and single-bed-unit (1984 to 1993) cohort periods is presented in **Table 1**.

We have used the same case definition of bacteremia (candidemia) as in our previous report.[1] Isolation of a species once or on multiple subsequent blood cultures was considered a case of infection with that organism (species). For mortality comparisons, a patient was categorized by the presence and types of organisms that caused positive findings on blood cultures.

Mortality predictions were made using logistic regression techniques described by Mason et al[1] for burned patients with no bacteremia. In the present study, a predictor was generated based on 1515 patients (with burns on ≥20% of body surface) admitted between 1974 and 1993 who did not have a positive blood culture during hospitalization. The analysis related patient outcome to burn size and age. The equation derived for this population is:

$$K = -4.985 + 0.1054(\%\ \text{Burn}) - 0.2279(\text{Age}) + 0.006122(\text{Age}^2) - 0.0000351(\text{Age}^3)$$

$$PM = e^K/(1+e^K)$$

where PM is predicted mortality. Predicted mortality for an individual is based on that individual's burn size and age. The estimate of the expected number of deaths within a patient group is the sum of the individual predicted mortalities for that group. Confidence limits for the group mortality estimate were derived by a binomial expansion technique. An example of a group prediction for the 1515 patients with no bacteremia is presented in the following tabulation:

Data	Value
No. of admissions	1515
No. (%) of predicted deaths	351(23.2)
95% confidence interval	328-374
No. of observed deaths	351
Observed-predicted mortality ratio	1.00

Based on our previous observation that gram-negative isolates from blood cultures had the greatest associated added mortality risk, we separated the population with bacteremia into patients with one or more cases of bacteremia (candidemia) and at least one culture positive for GNB and patients with cultures positive for gram-positive bacteremia only. Gram-positive cases were principally due to *Staphylococcus aureus*. Patients with one or more yeast species isolated from blood cultures were examined as an additional group. These patients were included in the gram-negative group as well if they also had GNB. Throughout the duration of this review, blood was cultured only for clinical indications of infection.

Table 1. Patient Demographics*

	Open-Ward Cohort (1974-1983)	Single-Bed Cohort (1984-1993)
No. of admissions	1605	914
Mean age, y	31.3	32.2
Mean total burn, % of body surface	47.5	42.8
Third-degree burns, %	22.6	22.5
Deaths, No. of patients	672	214
Mortality, % of patients	41.9	23.4

**Includes patients with burns of 20% or more of body surface.*

Table 2. Incidence of Blood Pathogens in Open-Ward (1974 to 1983) and Single-Bed (1984 to 1993) Cohorts

	Cohort Years, No. (%) of Patients		
Infections	1974-1983 (N=1605)	1984-1993 (N=914)	P*
Gram-negative	500 (31.2)	110 (12.0)	.001
Gram-positive	510 (31.8)	183 (20.0)	.001
Yeast	107 (6.7)	49 (5.4)	NS

**NS indicates not significant.*

ously open intensive care ward environment. We have documented that the occupation of this new facility was associated with a break in transmission of two on-going endemics. Well-characterized multiple-antibiotic-resistant strains of *Providencia stuartii* and *P aeruginosa* were eliminated by intentional cohort admission of new patients to the new unit. The break in patient-to-patient transmission is thought to have been facilitated by the move and also associated with changes in nurse staffing that limited cross trafficking between patients in their individual rooms.[6,7] Caregivers wore masks, gowns, and gloves while in contact with patients; these covers were removed and hands were washed when exiting patient rooms. A microbial surveillance system was used to document colonization by *P stuartii* and *Pseudomonas* strains, the presence of new resistant organisms, or any apparent cross contamination of patients with such organisms. This information was made available to caregivers so that possible breaks in isolation techniques could be rapidly identified and corrected. We have continued this microbial surveillance as an element of quality improvement.

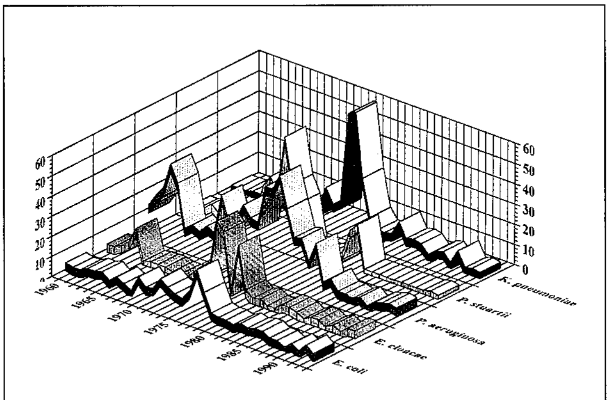
RESULTS

The predicted number of deaths in the population of 1004 patients with bacteremia was 405. The 95% confidence limits for this estimate were 381 and 429 deaths. The actual number of deaths among the patients with bacteremia was 535, a number well beyond the upper confidence limit. The ratio of observed mortality to predicted mortality was 1.32, a 32% increase above that expected on the basis of extent of injury and age. A comparison of the incidence of gram-negative, gram-positive, and yeast blood isolates for the two time periods is presented in **Table 2**.

Table 3. Incidence of Gram-negative Blood Pathogens in Patients With Burns*

Organism	Cohort Years, No. (%) of Patients 1974-1983	1984-1993	P†
Pseudomonas aeruginosa	268 (17.8)	31 (3.4)	.0001
Klebsiella pneumoniae	193 (12.0)	37 (4.0)	.0001
Enterobacter cloacae	99 (6.2)	18 (2.0)	.0001
Escherichia coli	76 (4.7)	26 (2.8)	.0206
Providencia stuartii	66 (4.1)	1 (0.1)	.0001

**Indicates patients with burns of 20% or more of body surface.*
†Comparisons are between cohort years.



Distribution of the principal gram-negative pathogens for which blood cultures were positive between 1959 and 1994. K pneumoniae *indicates* Klebsiella pneumoniae; P stuartii, Providencia stuartii; P aeruginosa, Pseudomonas aeruginosa; E cloacae, Enterobacter cloacae; *and* E coli, Escherichia coli.

A comparison of the incidence of the five most common gram-negative species in this 20-year period is presented in **Table 3**. As can be seen, all species were significantly less frequent in the second cohort. The incidence of these organisms over a 35-year period at this institution is presented in the **Figure**. Sporadic outbreaks of these pathogens stopped with the opening of the new single-bed unit. The numbers of blood cultures positive for bacteria, and in particular GNB, have been significantly reduced since that time. The incidence of cultures positive for yeast was similar in both groups.

The actual mortality in each of the organism groups was next compared with the predicted mortality. The results for gram-negative organisms are presented in **Table 4**. The predicted mortality was similar in both groups, with that in the later group slightly greater. As can be seen, the actual number of deaths in the open-ward cohort was 61% above that predicted. This result is essentially the same as that described in our earlier report.[1] The mortality associated with GNB in the later group is within the confidence limit of the prediction for patients without blood cultures positive for GNB. The number of postburn days to the first culture positive for GNB in the single-patient-room cohort was found to be more than twice that found in the earlier cohort (28.9 vs 11.8 days, respectively; $P<.001$). Mortality assessment of patients with candidemia is presented in **Table 5**. The increase in mortality associated with candidemia during the first period is similar to our previous finding. The increase in associated mortality was absent in the later group.

The results for patients with only gram-positive bacteremia during their hospitalization are presented in **Table 6**. These results also agree with those of our previous review. Gram-positive bacteremia, when not preceded or followed by cultures positive for GNB or yeast, was not associated with an increase in mortality above that predicted on the basis of extent of burn and age.

Table 4. Patients With Blood Cultures Positive for Gram-negative Isolates*

	Cohort Years 1974-1983	1984-1993
No. (%) of patients with gram-negative infection	500 (31)	110 (12)
Predicted mortality, No. (%) of infected patients	227 (45)†	54 (49)‡
Observed mortality, No. of patients	367	47
Observed-predicted mortality, ratio	1.61§	0.87‖

**Includes patients with burns of 20% or more of body surface.*
†Confidence interval was 209 to 244.
‡Confidence interval was 46 to 63.
§P<.0001.
‖Difference was not significant.

Table 5. Patients With Blood Cultures Positive for Candidemia*

	Cohort Years 1974-1983	1984-1993
No. (%) of patients with candidemia	107 (6.7)	49 (5.4)
Predicted mortality, No. (%) of infected patients	53 (50)†	26 (53)‡
Observed mortality, No. of patients	85	27
Observed-predicted mortality, ratio	1.60§	1.04‖

**Includes patients with burns of 20% or more of body surface.*
†Confidence interval was 44 to 62.
‡Confidence interval was 20 to 33.
§P<.0001.
‖Difference was not significant.

Table 6. Patients With Blood Cultures Positive for Gram-positive Isolates*

	Cohort Years 1974-1983	1984-1993
No. (%) of patients with gram-positive infections	218 (13.6)	117 (12.8)
Predicted mortality, No. (%) of patients	61 (28)†	36 (31)‡
Observed mortality, No. of patients	57	28
Observed-predicted mortality, ratio§	0.93	0.78

**Includes patients with burns of 20% of body surface.*
†Confidence interval was 50 to 72.
‡Confidence interval was 28 to 44.
§Differences were not significant.

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COMMENT

Control of infection has been a goal in burn care since the development of the germ theory. There is, however, no consensus on the most appropriate infection control program for serious burns.[8-10] The purpose of this report is not to make specific claims for the design of this burn center or for our institution's specific methods of patient isolation and infection control, but to demonstrate that reduction in the incidence of blood infections has fulfilled a prediction in our previous review. Improvement in control of GNB has been associated with an improvement in mortality comparable to the previous increment in mortality attributable to such infections.

The improvement in outcome for the fewer patients that still become infected with gram-negative organisms is less easy to explain. Early excision, improved ventilation techniques, nutritional support, and other treatments and support techniques continue to improve patient care. It seems possible that the reduction in GNB has reduced a morbid complication that has traditionally clouded the true benefit of improved techniques of physiological support. We have previously reported on the significance of *P aeruginosa* infections during the history of our burn center and have shown that the incidence of *P aeruginosa* infections was reduced and the associated mortality decreased after the use of single-patient rooms.[4,7,11] These differences were associated with a much later postinjury time of infection, which was thought to explain in part the improved survival. Patients with delayed colonization and infection appear to represent a less susceptible patient population in which response to infection is more effective. The delay in time of infection documented in this study allows patients to have a longer exposure to the benefits of such treatments and reach a stage of recovery in which response to infection is more effective. Isolation from cross contamination closes the window of susceptibility to infection and appears to shift the balance between microbial pathogenicity and host resistance in favor of the patient.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

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DISCUSSION

David N. Herndon, MD, Galveston, Tex: The authors are to be congratulated on this huge and excellent review of infections and morbidity and mortality in burns over 20% total body surface treated at their institution over the last 20 years. Their results are incontrovertible and will serve as a landmark reference for years to come.

The marked decrease in mortality noted in the current decade vs the previous decade has been reported by other observers, including ourselves, and in a recent collection of mortality data from a variety of burn units performed by Saffle and reported at the American Burn Association [Saffle J, Davis B, Sullivan J, Williams P, The American Burn Association Patient Registry. Improved survival from thermal injury: data from the ABA Burn Patient Registry. *Proc Am Burn Assoc.* 1994;26:105]. The other units reporting improvements in survival, in contrast, had no changes in hospital design or infection control procedures in the year 1983, as described by Dr McManus. Rather, they attribute their observed decreases in mortality, which are remarkably similar to the decreases in mortality described here, to improvements in early excision of the burn wound, early enteral feeding with decreased utilization of parenteral hyperalimentation, improved ventilatory support techniques, utilization of perioperative antibiotics, and more aggressive rehabilitation. These advances have contributed, clearly, to a decrease in length of hospital stay—in these reports—for major burns of 50% in the latter decade vs the former decade. Most burn specialists would predict that the greatest contributor to decreased infections and mortality in this decade has not been change of architecture of a burn unit or infection control techniques, but has been early closure of the burn wound.

Have the authors performed a logistic equation using the rate of wound closure as a factor to determine the degree to which this revolutionary and dramatic change in burn care has affected mortality?

Environmental control or single-bed care may indeed be very important issues. However, randomized prospective studies are required to substantiate independent treatment effects.

Dr McManus: Thank you, Dr Herndon, for your questions and discussion. We certainly agree with you that burn care has improved and mortality has decreased throughout the United States during this past decade. In our own particular instance, we noted this same trend and actually a significant improvement in survival and reported it to this Society in 1986, 1 year after the opening of our new unit. Our early excision practices had not changed when that improvement in survival was reported.

I do not want to argue that the differences that we've shown you in infection are completely unrelated to early excision. I think that early excision is perhaps the greatest improvement that has occurred in the treatment of burns since the development of topical antimicrobial burn creams. But in our case, we noted an improvement in survival with the break in the two endemics that were ongoing when we opened this unit.

And as I stated, I do not propose that this paper is to argue for a specific design of a burn unit. I think it does show you that gram-negative infections, as measured by bacteremia, can be controlled by improved patient care and by isolation.