Mortality of Bullous Skin Disorders From 1979 Through 2002 in the United States

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Objectives: To identify and analyze trends in bullous disease mortality from 1979 through 2002 in the United States.

Design: Retrospective population-based analysis.

Setting: Mortality records from the Centers for Disease Control and Prevention mortality database.

Participants: Mortality records from 1979 through 2002 for persons who died of bullous disease.

Main Outcome Measures: Age-adjusted mortality rates and trends for 4 bullous disease subgroups: toxic epidermal necrolysis, pemphigoid, pemphigus, and epidermolysis bullosa.

Results: The overall age-adjusted (to the 2000 US standard population) annual mortality rate from bullous diseases of the skin was 0.103 death per 100 000. The average mortality from bullous disorders was 0.098 per 100 000 in 1979 through 1982 and remained stable at 0.099 per 100 000 during the final 4 years of the study, 1999 through 2002. Pemphigoid had a significant increase in mortality from 1979 through 2002, while pemphigus demonstrated a significant decrease in mortality. The mortality rate for toxic epidermal necrolysis was much higher among blacks (0.192 death per 100 000) than whites (0.025 per 100 000) (P < .001), with a mortality rate ratio of 7.57 (95% confidence interval, 6.97-8.21).

Conclusions: Overall mortality from bullous diseases remained stable from 1979 through 2002, although an increasing mortality from pemphigoid and a decreasing mortality from pemphigus occurred during this period. A very large racial disparity in mortality from toxic epidermal necrolysis was observed.
Mortality rates were analyzed by both sex and race by means of StatXact (version 3.1; Cytel Software Corp, Cambridge, Massachusetts). Linear regression was performed to assess trends in death rates over time by means of SPSS statistical software (version 17.0; SPSS Inc, Chicago, Illinois). \( P < .05 \) was considered to be statistically significant. Institutional review board approval was not applicable to this study because it used publicly available data.

A total of 5848 deaths were attributable to bullous diseases in the United States from 1979 through 2002. The overall age-adjusted (to the 2000 US standard population) annual mortality rate from bullous diseases of the skin was 0.103 death per 100,000. A total of 2378 deaths in the 24-year period that we examined were from TEN. During this same period, pemphigoid led to 1530 deaths, pemphigus to 1226 deaths, and epidermolysis bullosa to 714 deaths; the age-adjusted mortality rate for TEN was 0.041 death per 100,000, whereas the age-adjusted mortality rates for pemphigoid, pemphigus, and epidermolysis bullosa were 0.028, 0.023, and 0.011 per 100,000, respectively.

Mortality varied by age, with pemphigoid and pemphigus having the highest concentration of deaths among the very old. Deaths were also concentrated among the elderly for patients with TEN, although less so than for pemphigoid and pemphigus. Death from epidermolysis bullosa occurred almost exclusively among infants, and there was a very small proportion of TEN deaths among infants as well (Table).

During the first 4 years of the period studied (1979-1982), the average mortality from bullous disorders was 0.098 death per 100,000, and during the last 4 years of the period (1999-2002), the average mortality from bullous diseases was similar, 0.099 per 100,000. For some of these disorders, age-adjusted mortality rates varied over time during this 24-year period. For pemphigoid we noted a significant increase of 0.0055 death per 100,000 per decade (95% confidence interval [CI], 0.0025-0.0086 per 100,000; \( F = 14.6, P = .001 \)), from 0.020 in 1979-1982, to 0.029 twenty years later. By contrast, there was a significant decrease in the age-adjusted mortality rate for pemphigus of 0.0066 death per 100,000 per decade during the study period (95% CI, −0.0096 to −0.0041 per 100,000; \( F = 26.5, P < .001 \)). This change reflects a decrease from 0.033 in 1979-1982 to 0.021 in 1999-2002. Linear regression failed to show any significant changes in mortality trends from 1979-2002 for TEN or for epidermolysis bullosa (Figure).

The mortality rate for TEN was much higher among blacks (0.192 death per 100,000) than whites (0.025 per 100,000) \( (P < .001) \), with a mortality rate ratio of 7.57 (95% CI, 6.97-8.21). The relative risk of death from TEN for black females vs black males was 1.40 \( (P < .001; 95\% \text{ CI}, 1.21-1.60) \), whereas the relative risk of death from TEN for white females vs white males was 1.16 \( (P < .01; 95\% \text{ CI}, 1.03-1.30) \).

Mortality rates were also higher among blacks than whites for pemphigoid (0.051 vs 0.026 death per 100,000; \( P < .001 \)). The relative risk of death from pemphigoid in blacks vs whites was 1.95 \( (P < .001; 95\% \text{ CI}, 1.68-2.25) \), and females were at slightly increased risk of death...
from pemphigoid (relative risk, 1.18; \( P = .004; 95\% \) CI, 1.06-1.32).

Blacks had higher mortality rates for pemphigus than whites (0.030 vs 0.022 death per 100,000), and their relative risk of death was 1.38 (\( P < .001; 95\% \) CI, 1.16-1.65). There was no significant difference in risk of death from pemphigus by sex.

The mortality rate for blacks was similarly higher than that for whites in the epidermolysis bullosa group (0.016 vs 0.011 death per 100,000), and blacks were 1.44 times as likely as whites to die of epidermolysis bullosa (\( P < .001; 95\% \) CI, 1.20-1.73). Females had a slightly increased risk of death from epidermolysis bullosa (relative risk, 1.23; \( P = .007; 95\% \) CI, 1.06-1.43).

This study of mortality from bullous disorders during a 24-year period found that pemphigoid mortality increased while mortality from pemphigus decreased. A very large racial disparity in mortality from TEN was observed.

A recently published study identified that the incidences of bullous pemphigoid and pemphigus vulgaris are increasing in the United Kingdom,\(^{17}\) but changes in incidence of pemphigoid and pemphigus in the United States are unknown, as is their effect on mortality rates. Several prospective and retrospective studies have evaluated prognostic factors in patients with bullous pemphigoid, and the type of therapy patients have received has not been found to be related to overall prognosis or mortality.\(^ {2,4,6,12,16-18} \) There is also no obvious relationship between the introduction of the limited number of agents used to treat bullous pemphigoid and the shifts in mortality during the period studied. Thus, changes in therapy may not be contributing to the observed increase in bullous pemphigoid death rates. Indeed, a recent study found little impact in overall mortality due to bullous pemphigoid.\(^ {9} \) A retrospective study by Carson et al\(^ {19} \) suggested that mortality from pemphigus decreased significantly with the addition of adjuvant therapy (azathioprine, cyclophosphamide, methotrexate, and gold) to corticosteroids during the period from 1969 through 1991. Further introduction of plasmapheresis and then intravenous immunoglobulin in the mid-1990s for treatment-refractory cases may have also contributed to declining mortality.\(^ {10-22} \)

Mortality for black persons was significantly higher for every bullous disease studied and was particularly marked in the TEN group of disorders, but the cause, perhaps including social or other factors, cannot be determined from our data.

This study provides a broad descriptive analysis of trends in bullous disease mortality in the United States during the 24-year period from 1979-2002 through interpretation and analysis of national mortality records. Key strengths include the use of a large population-based data source covering billions of person-years of observation using routine death certification, and the ability to use these data to assess trends over a quarter-century. The size of the population and the duration of the observation period allow examination of issues that might not otherwise be assessable. However, there were several limitations of our investigation. First, the accuracy of the reporting of deaths from bullous disorders was not independently verified. Hence, we may have overestimated or underestimated the true mortality of these disorders or the trends in rates. Second, the classification schemas used to report the diseases may also lead to inaccurate measurements of mortality rates. This is particularly possible in the classification of epidermolysis bullosa with the ICD-9 code of 757.3, which covers a broad range of skin diseases beyond epidermolysis bullosa alone. Therefore, mortality attributable to this group of disorders may be overestimated for the years 1979 through 1998. Finally, very little information about the persons who died of these diseases was available for analysis, and therefore interpretation of the findings is limited to rather broad speculation about the factors driving the trends observed.

We have provided an overview of trends of bullous skin diseases that demonstrates significant shifts in mortality for both pemphigus and pemphigoid, and important racial discrepancies in mortality. Although this study perhaps raises more questions than it answers, we hope it will serve as a springboard to the investigation of the causes of these trends so that dermatologists, internists, and other specialists will be better able to reduce bullous disease mortality in the future.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Weinstock. Acquisition of data: Risser, Lewis, and Weinstock. Analysis and interpretation of data: Risser, Lewis, and Weinstock. Drafting of the manuscript: Risser and Weinstock. Critical revision of the manuscript for important intellectual content: Risser and Weinstock. Statistical analysis: Risser, Lewis, and Weinstock. Study supervision: Weinstock.

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REFERENCES


17. Vinayagar Medical College, Puducherry, India. The correct answer to our June challenge was multiple leiomyomatosis. For a complete discussion of this case, see the Off-Center Fold section in the July Archives (Kovalyshyn I, Spencer PS, Busam KJ, Marghoob AA. Multiple tender papules in a 48-year-old man. Arch Dermatol. 2009;145(7):829-834).

18. Be sure to visit the Archives of Dermatology Web site (http://www.archdermat.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.