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Incidence and Mortality Rates of Bullous Pemphigoid in Olmsted County, Minnesota, Over 6 Decades

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Abstract

Background—Bullous pemphigoid (BP) is an autoimmune blistering disease that is associated with an increased mortality rate.

Objective—To determine the incidence and mortality rate of patients with bullous pemphigoid.

Methods—Eighty-seven residents of Olmsted County, Minnesota, were identified who had their first lifetime diagnosis of BP from January 1960 – December 2009. Incidence and mortality rate were compared to age- and sex-matched control patients from the same geographic area.

Results—The adjusted incidence of BP was 2.4 per 100,000 person-years (95% CI, 1.9–2.9). Incidence of BP increased significantly with age (P<.001) and over time (P=0.034). Trend tests indicate increased diagnosis of localized disease (P=.006) may be a contributing factor. Survival observed in the incident BP cohort was significantly poorer than expected (P<.001). Survival was not different among patients with multisite vs localized disease (P=.90).

Limitations—Retrospective study design and study population from a small geographic area.

Conclusion—Incidence of BP in the United States is comparable to that found in Europe and Asia. The mortality rate of BP is lower in the United States than Europe, but higher than previous estimates.

Keywords

Bullous pemphigoid; autoimmune blistering disorder; epidemiology; incidence; mortality; geriatric

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Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering dermatosis[1] and has increased prevalence in the elderly population.[2] Most large population studies of BP incidence and mortality rate have been performed in Europe,[3] but there is a paucity of comparable data from the United States.[4–6]

The incidence of BP appears to be increasing, with previous values approximating 6 or 7 cases per 1 million persons per year in Europe;[7,8] vs more recent numbers ranging from 10 to 43 cases per 1 million persons per year[9–11]. A French cohort of nearly 4 million persons, showed 21.7 cases per 1 million persons per year—a 3-fold increase in incidence during the past 15 years.[1,3] No analogous US studies have assessed BP incidence.

Multiple case series have shown increased mortality rates in patients with BP compared with an age-, sex- and location-matched population, beginning with early series, such as Savin[12,13] and Roujeau et al,[14] but controversy continues over whether this is a true association with the disease or is due to multiple confounding factors associated with an aging population (eg, medical comorbidities, infection, hospitalization, exposure to certain medications).

Previous US data have showed lower mortality rates associated with BP in the United States than in Europe. The largest US-based series,[5] which evaluated 223 patients, did not find an increased mortality rate in BP patients. However, the control group was based solely on age-matched US population control subjects, whose characteristics may have differed substantially from the regional study cohort.[16] Another series used International Classification of Diseases (ICD)-9 and ICD-10 codes as listed on death certificates from a publicly available national database but did not verify diagnosis through a case or chart review.[6]

The purpose of the present study was to determine the age-stratified incidence of BP in Olmsted County, Minnesota, from 1960 through 2009 and to compare survival of these patients with that of an analogous age- and sex-matched population in Minnesota.

Materials and Methods

This study was approved by the institutional review boards of Olmsted Medical Center and Mayo Clinic and Declaration of Helsinki protocols were followed. We used the Rochester Epidemiology Project, a centralized, medical records linkage system containing medical diagnoses for nearly all patients in Olmsted County. This population has been shown to be demographically similar to the general US white population.[45–47] It also has a relatively low emigration rate,[45] which facilitates acquisition of complete patient follow-up data.

Through the Rochester Epidemiology Project, all medical records for all patients receiving a first-ever diagnosis of BP (based on search with terms “bullous pemphigoid” and “pemphigoid”) between January 1, 1960, and December 31, 2009, were identified and retrieved. Diagnosis of BP was confirmed based on combined review of the clinical presentation and laboratory evidence, including any of the following: 1) histopathologic

findings, 2) direct immunofluorescence study showing linear deposition of antibody or complement (ie, immunoglobulin G [IgG] or C3, or both), 3) indirect immunofluorescence detecting circulating IgG antibodies against basement membrane proteins, or 4) positive BP180 or BP230 IgG antibody measured with enzyme-linked immunosorbent assay (ELISA). Cases in which the clinical presentation was atypical (eg, urticarial, erosion, crust/scale) were included when there was sufficient supporting objective laboratory data to support BP. Cases of cicatricial pemphigoid were excluded. Patients with oral disease or predominant oral disease only were excluded to avoid including bullous diseases caused by different auto-antibodies.

Incidence rates were obtained by considering incident cases of BP as the numerator and age- and sex-specific population counts from Olmsted County, Minnesota, as the denominator. Population counts for 1960 through 2000 were estimated using census data from 1960, 1970, 1980, 1990, and 2000, with linear interpolation for intercensal years. The populations at risk for 2001 through 2009 were obtained from US Intercensal Estimates.[48] Because nearly all of the population of Olmsted County is white, incidence rates were directly age- and sex-adjusted to the structure of the US white population in the year 2000. Incident cases were grouped into intervals on the basis of age at diagnosis (0–39, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years) and the year of diagnosis (1960–1969, 1970–1979, 1980–1989, 1990–1999, and 2000–2009). The relations of age at diagnosis, sex, and year of diagnosis with the incidence of BP were assessed by fitting Poisson regression models (GENMOD procedure; SAS Institute Inc).

Overall survival was estimated with the Kaplan-Meier method and compared among groups through log-rank tests. The duration of follow-up was calculated from the date of diagnosis to the date of death or last follow-up. Overall survival was compared with the survival expected in the Minnesota white population on the basis of age at diagnosis, sex, and year of diagnosis with the cohort method.[49]

Localized disease was characterized as single site (eg, scalp, neck, limbs, chest). Generalized disease was characterized as involvement at more than 1 site. Trends in the diagnosis of localized disease and atypical clinical presentations over time were evaluated using Cochran-Armitage trend tests.

Statistical analyses were performed with a software package (SAS Institute Inc). All tests were 2-sided, and *P* values less than .05 were considered statistically significant.

Results

BP Incidence

Characteristics collected from the 87 incident cases of BP are summarized in Table 1. The mean age at diagnosis was 74.5 years. The age- and sex-adjusted incidence of BP was 2.4 per 100,000 person-years (95% CI 1.9–2.9). The age-adjusted incidence was 2.2 per 100,000 person-years (95% CI, 1.6–2.8) for women compared with 2.8 per 100,000 person-years (95% CI, 1.8–3.7) for men (*P*=.25). The incidence of BP increased significantly with age at diagnosis (*P*<.001) (Figure 1) and over time (*P*=.034) (Table 2 and Figure 2). There was no

statistically significant evidence that the increase in incidence over time differed between men and women (*P*=.93) or by age (*P*=.47). There was not a statistically significant difference in age at diagnosis among the time periods of the study (p=0.82). A trend test for localized vs generalized disease by diagnosis year indicated that the diagnosis of localized disease became more common over time (*P*=.006). In looking at bullous presentation vs atypical clinical presentations, a trend test was not significant for nonbullous presentations being diagnosed more frequently over time (*P*=.13).

Mortality Data

At last follow-up, 66 patients had died, at a mean of 4.5 years after BP diagnosis (median [range], 2.6 years [6 days–37 years]). The mean duration of follow-up for the 21 patients who were still alive at last follow-up was 6.7 years (median [range], 5.0 years [1 month-21 years]). Of the 21 patients who were still alive at last follow-up, 6 had fewer than 1 year of follow-up. Estimated overall survival rates (95% CI; number still at risk) at 1, 2, 4, 6, 8, and 10 years after the diagnosis were 81% (73%–90%; 65), 68% (59%–79%; 53), 47% (37%–60%; 36), 33% (24%–46%; 23), 25% (16%–37%; 16), and 21% (13%–33%; 11), respectively. By comparison, survival rates at these time points expected in the Minnesota white population were 92%, 84%, 71%, 58%, 48%, and 39%, respectively. The survival observed in the incident BP cohort was significantly poorer than expected (*P*<.001) (Figure 3). Given the same distributions of age and sex, about 35 deaths would have been expected in the Minnesota white population, resulting in a standardized mortality ratio of 1.90 (95% CI, 1.47–2.42).

Estimated overall survival rates (95% CI; number still at risk) at 1, 2, 4, 6, and 8 years after diagnosis for the 12 patients with localized disease were 91% (75%–100%; 8), 80% (58%–100%; 6), 48% (22%–100%; 3), 32% (10%–98%; 2), and 32% (10%–98%; 2), respectively. Estimated overall survival rates (95% CI; number still at risk) at 1, 2, 4, 6, 8, and 10 years after diagnosis for the 73 patients with generalized disease were 79% (70%–89%; 55), 67% (57%–79%; 46), 47% (36%–60%; 32), 33% (24%–46%; 21), 23% (15%–36%; 14), and 22% (14%–35%; 11), respectively. There was not a statistically significant difference in overall survival among patients with localized vs those with generalized disease (*P*=.90).

Estimated overall survival rates (95% CI; number still at risk) at 1 year following diagnosis were 75% (43%–100%; 3), 75% (50%–100%; 5), 85% (67%–100%; 11), 78% (65%–93%; 28), and 87% (73%–100%; 18) for patients who had the diagnosis in 1960 through 1969, 1970 through 1979, 1980 through 1989, 1990 to 1999, and 2000 through 2009, respectively (*P*=.77).

Two patient were missing treatment information; of the other patients, 62 (73%) were taking systemic immunosuppressive agents.

Discussion

BP Incidence

Whereas the incidence of BP appears to be increasing in Europe,[1,3,17,18] there are no prior incidence studies reported in the United States. Our data show the incidence of BP at 2.4

cases per 100,000 person-years, which is on par with or higher than most of the recent European reports. It has been proposed by other investigators that the increased BP incidence is attributable to a greater proportion of older persons in the general population.[3,11] We found the age-adjusted incidence increased over time across all age-groups, arguing against the hypothesis that the increasing proportion of elderly persons is the sole reason for increased incidence of BP.

Another proposed explanation for the increase in BP incidence is the concomitant increase in the prevalence of neurodegenerative disorders,[19] because many reports have implicated disorders such as dementia, stroke, and Parkinson disease as risk factors for BP development.[20,21] It is conceivable that increased use of medications such as diuretics and neuroleptics, which are often implicated as triggers for BP, could also contribute, although this hypothesis was not evaluated in this study. In addition, many other autoimmune diseases have increased in incidence in recent decades, such as rheumatoid arthritis in the same Olmsted County population,[22] diabetes mellitus type 1,[23] and myasthenia gravis.[24]

Rarer forms of BP, such as pemphigoid nodularis, eczema-type, dyshidrosiform-type, and others, comprised 21% of the cases reported by Joly et al.[3] In the present study, all 6 patients without classic clinical findings of BP received the diagnosis in the 1990s. The increased incidence seems less likely due to increased sensitivity of laboratory testing.[11,25] Only 4 patients in this study had ELISA performed, so our findings are not likely attributable to enhanced detection through ELISA methods.[26] Moreover, it may be debated whether diagnostic sensitivity with NC16A-directed BP180 ELISA testing is superior to clinical criteria plus direct immunofluorescence or indirect immunofluorescence, or both, in some cases.[27,28]

Some authors have studied the rate of diagnosis of BP based on tissue specimen diagnosis as a proxy for clinical diagnosis and observed no change in incidence over time.[29] Although that study design was a simple way to address the question of BP incidence, it is unclear whether tissue specimen diagnosis correlates directly with clinical disease incidence.

There are several limitations to this study. The study population is from a small geographic area that is predominantly white and may not be generalizable. Given the long time frame of the study, knowledge and recognition of BP and treatment regimens have changed over time. Increasing awareness of the disease entity and therefore increased diagnosis may be contributing to the increasing incidence.

Mortality Rate

Our data showed a 19% 1-year mortality rate for patients with BP during the previous 50 years, which straddles previous reports from Europe (13%–41%) and the United States (11%–23%). Table 3 summarizes findings from large mortality studies from the past 40 years. It is notable that the most recent mortality figures from France[3] are nearly double that observed in our study. As hypothesized previously, older age at diagnosis (74.5 years in our series vs 82 years) and poorer general medical condition may be to blame for the greater mortality rate reported in Europe.[3] This hypothesis is supported by Rzany et al,[30] who found that increased age (average of 80 years), greater dosage of oral glucocorticoids at hospital

discharge, and low serum albumin level as a proxy measure for overall medical condition[31] were associated with a significantly higher fatality rate within the first year following hospitalization. Some authors have also asserted that patient selection bias has led to the differences in reported mortality rates[32] and cite also the lack of age- and comorbidity-matched control subjects as limitations to estimating actual disease-specific mortality rate.[33] Selection bias inherent in studies examining patients at major tertiary referral centers was averted in our study with the use of a population-based study design.[4]

In previous studies, no factors directly related to BP, such as extent of lesions, were found to affect overall survival. Actual survival predictors were related more to underlying demographic characteristics, including older age or female sex, and associated medical conditions, such as cardiac insufficiency, history of stroke, and dementia, along with a low Karnofsky performance score.[34] We also did not find a statistically significant difference in overall survival among patients with localized disease vs those with generalized disease. However, it is noted that those patients with generalized disease had a higher 1-year mortality rate.

Death due to sepsis in a more frequently hospitalized, immunosuppressed elderly population has also been proposed as a reason for the increased mortality rate in Europe.[4] This reason was refuted by a population-based study in Spain, in which only 2 of 11 patients died of sepsis during the study period and neither death was within 6 weeks of initial hospitalization for BP.[35] In addition, there was no difference in the length of hospitalization for the 11 patients who died, making it unlikely that these parameters could account for greater mortality rates in all settings[36] —although this may have been the case in other European series.[15] However, data on patients from the same Olmsted County population as the present study have showed that death due to sepsis was significantly more likely to occur in patients with BP than with matched control subjects.[37]

Increased mortality rate due to oral corticosteroid use at dosages greater than 0.5 mg/kg per day (and concomitant longer hospital stays) in comparison with topical corticosteroid use has also been reported.[7,15] We were not able to compare mortality rates in patient on immunosuppressive medications versus other treatments in the current study. The present population-based, longitudinal study provides evidence for the reported increased incidence of BP over time. Although explanation for the increased incidence is not readily identified, our findings raise the possibility that increased diagnosis of localized disease over time may have a role. We found that extent of disease did not contribute to differences in overall survival.

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Abbreviations

BP	bullous pemphigoid

ELISA	enzyme-linked immunosorbent assay
ICD	International Classification of Diseases
IgG	immunoglobulin G

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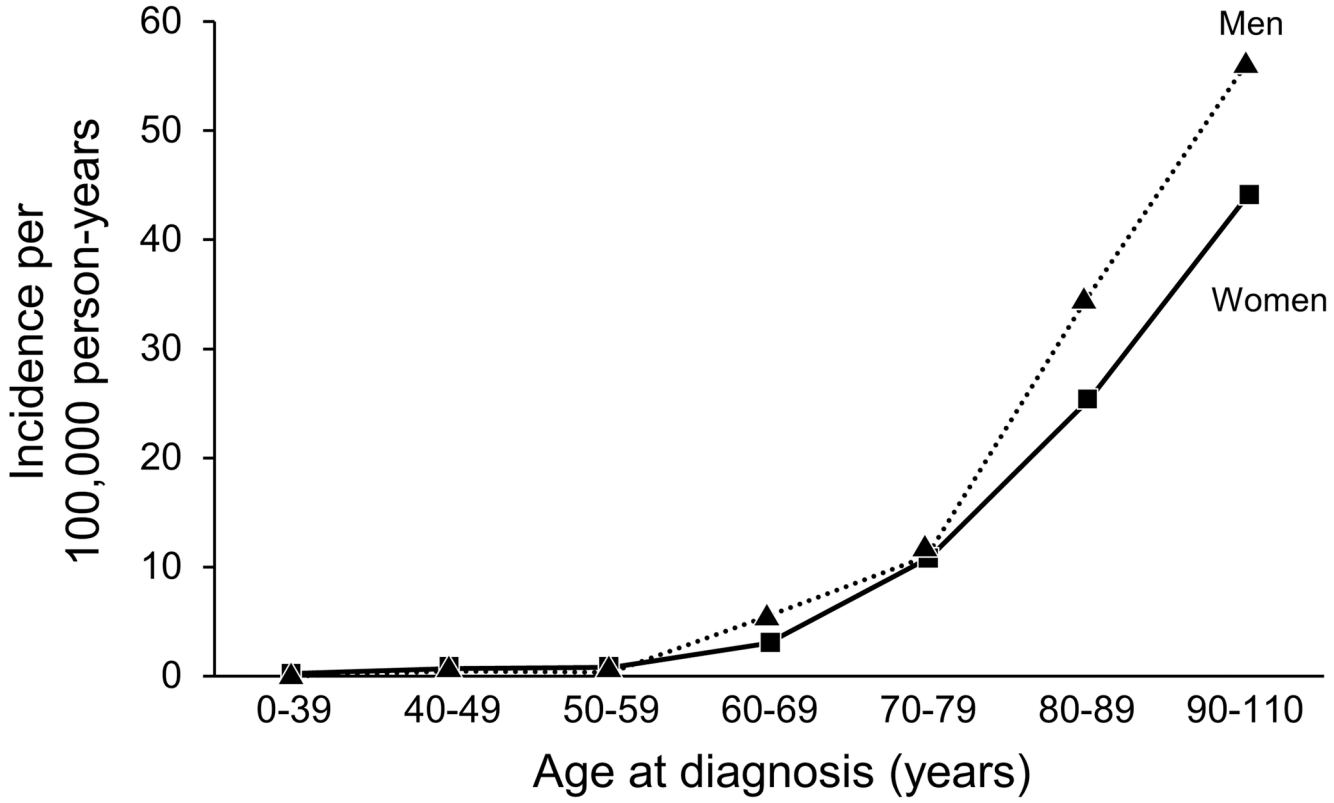

Figure 1.
Bullous Pemphigoid. Incidence of BP Showing Significant Increases With Age at Diagnosis.

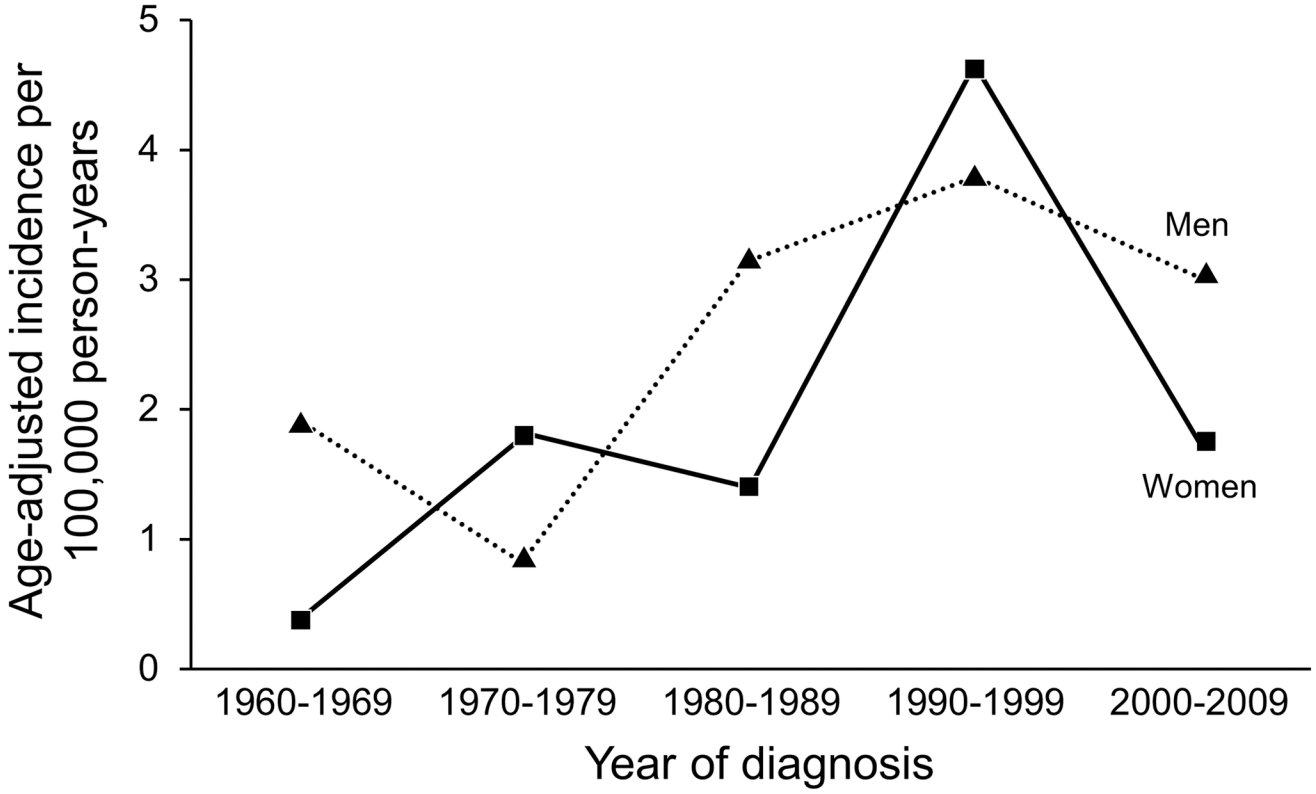

Figure 2.
Bullous Pemphigoid. Incidence of BP Showing Significant Increase Over Time.

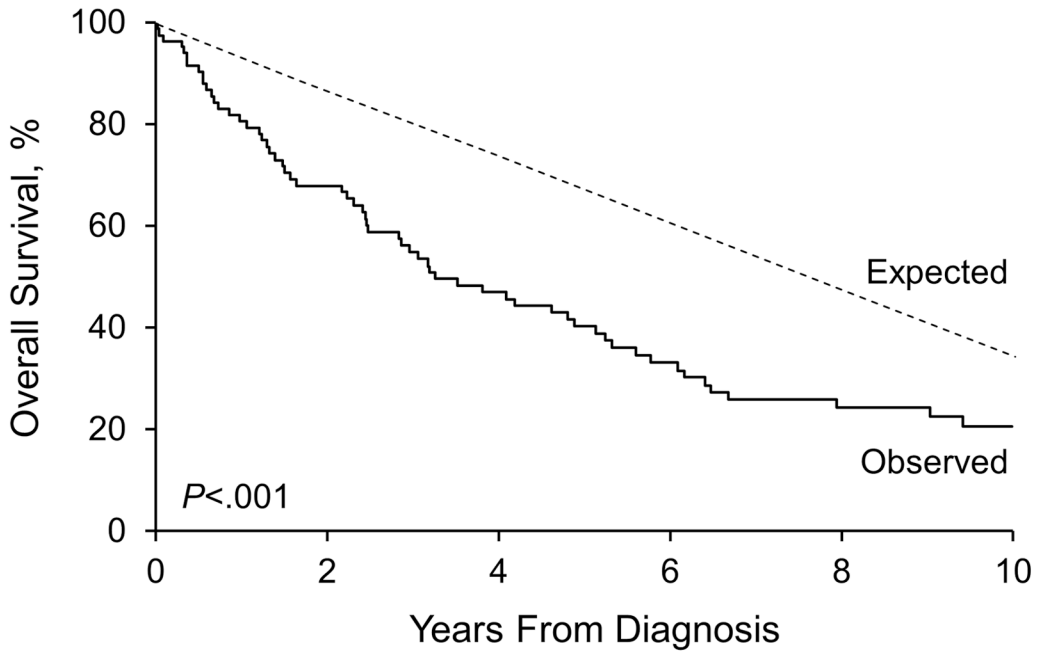

Figure 3.
Bullous Pemphigoid. Survival in the Incident BP Cohort With Significantly Poorer Than Expected Results.

Table 1

Summary of 87 Incident Cases of Bullous Pemphigoid

Characteristics	Value	No. of Patients
Age at diagnosis, y		
Mean (SD)	74.5 (12.2)	
Median (range)	79 (41–100)	
Time from symptom onset to diagnosis, mo (n=86)		
Mean (SD)	7.2 (14.8)	
Median (range)	2 (0–76)	
Weight, kg (n=86)		
Mean (SD)	75.0 (15.6)	
Median (range)	73 (48–135)	
Age at diagnosis, y		
0–39		0
40–49		3
50–59		3
60–69		14
70–79		24
80–89		32
≥90		11
Sex		
Female		50
Male		37
Year of diagnosis		
1960–1969		4
1970–1979		8
1980–1989		13
1990–1999		36
2000–2009		26
Race/ethnicity (n=84)		
White		78
African American		4
Other		2
Residency at diagnosis		
Rochester		84
Balance of Olmsted County		3
Clinical department that made diagnosis (n=85)		
Dermatology		82
General medicine		2
Other		1
Referral to dermatology service (n=65)		
No		11

Characteristics	Value	No. of Patients
Yes		54
Method of diagnosis		
Histology + direct IM + indirect IM		42
Histology + direct IM		29
Direct IM		4
Histology		3
Histology + indirect IM		3
Histology + direct IM + indirect IM + BP180/BP230		2
Indirect IM		1
Direct IM + indirect IM		1
Indirect IM + BP180/BP230		1
Histology + direct IM + BP180/BP230		1
Direct IM (n=83)		
Positive		79
Negative		4
Indirect IM (n=57)		
Positive		57
Negative		0
Exposure to therapy (n=86)		
Taking medications, but none listed previously		58
Furosemide		10
Penicillin		8
Captopril		3
Sulfa		3
None		2
UV radiation		2
Initial extent of disease (n=85)		
Limbs		74
Flexure		58
Chest		48
Back		35
Neck		22
Scalp		9
Face		9
Genitals		6
Oral cavity		5
Initial extent of disease (n=85)		
Localized		12
Generalized		73
Predominant appearance of lesions		
Blistered and denuded		76
Urticarial		6

Characteristics	Value	No. of Patients
Erosion		4
Crusted or scaly		1

Table 2

Incidence of Bullous Pemphigoid in Olmsted County, Minnesota, 1960–2009

	Female Patients		Male Patients		Total Patients		
Year of Diagnosis	No.	Rate[a]	No.	Rate[a]	No.	Rate[b]	95% CI
1960–1969	1	0.4	3	1.9	4	0.9	0.0–1.8
1970–1979	6	1.8	2	0.8	8	1.6	0.5–2.6
1980–1989	6	1.4	7	3.1	13	2.0	0.9–3.2
1990–1999	25	4.6	11	3.8	36	4.2	2.8–5.6
2000–2009	12	1.8	14	3.0	26	2.2	1.4–3.1

[a] Incidence per 100,000 person-years, age-adjusted to US white population in the year 2000.

[b] Incidence per 100,000 person-years, age- and sex-adjusted to US white population in the year 2000.

Table 3

Compilation of Large Prospective and Retrospective Studies on Mortality Rate in Bullous Pemphigoid

Authors of Study (Year)	Location	No. of Patients	Average Age, y	1-y Mortality Rate, %	Oral Corticosteroids, % of Patients
Europe and Asia					
Venning and Wojnarowska,[38] 1992	United Kingdom	82	74	19	70
Bernard et al,[1] 1995	France	78	80	38	NA
Roujeau et al,[14] 1998	France	217	79	41	79
Joly et al,[15] 2002	France	341	81	30	51
Rzany et al,[30] 2002	Germany	369	77	29	86
Garcia-Doval et al,[35] 2005	Spain	26	77	40	54
Gudi et al,[18] 2005	Scotland	83	79	25	NA
Joly et al,[34] 2005	France	170	83	26	0
Cortés et al,[39] 2011	Switzerland	115	80	21	66
Joly et al,[3] 2012	France	312	82	38	NA
Cortés et al,[40] 2012	Switzerland	60	80	27	89
Gual et al,[41] 2012	Spain	101	78	13	77[a]
Zhang et al,[42] 2013	China	94	NA	23	85
Li et al,[43] 2013	China	140	64	13	72
United States					
Fivenson et al,[44] 1994	Cincinnati, Ohio, Detroit, Michigan	18	78	12	NA
Colbert et al,[4] 2004	Milwaukee, Wisconsin	37	77	11	76
Parker et al,[5] 2008	United States	223	75	23	19[b]
Brick et al (present study)	Olmsted County, Minnesota	87	75	19	58[c]

Abbreviation: NA, not available.

[a] Of patients who died during the study, 77% (10/13) were receiving immunosuppressants.

[b] Among patients, 19% took systemic corticosteroids alone; 60% took corticosteroid-sparing agents, but it is unclear which of these patients were also taking corticosteroids.

[c] All 62 patients taking a systemic immunosuppressant medication were included in the data analysis.