Mortality Rate of Bullous Pemphigoid in a US Medical Center

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All patients at the Medical College of Wisconsin Affiliated Hospitals with a new diagnosis of bullous pemphigoid (BP) between May 1, 1997 and September 1, 2002 were included in this study. The age at onset, date of death or date of last follow-up visit, mode of treatment, co-morbidities, and initial and follow-up hospitalizations were noted. Thirty-eight new patients were identified and complete follow-up data were obtained on 37 of the patients. Patients were followed a minimum of 1 y or until the time of death. The mean duration of follow-up was 20 mo. Kaplan–Meier analysis of our population indicated a 1-y survival probability of 88.96% (standard error 5.21%), with a 95% confidence interval (75.6%, 94.2%). This survival rate was considerably higher than that recently reported in several studies from Europe (29%–41% first year mortality). Although the age at onset and co-morbidities of our patients were similar to those in the European studies, the rate of hospitalization of our patients was much lower than that of patients from Europe (1.5 d per patient *vs* 11–25 d per patient). This study suggests that differences in practice patterns may be an important factor in the reduced mortality rate in US BP patients compared with Europe.

Key words: bullous pemphigoid/mortality/autoimmunity
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Bullous pemphigoid (BP) is the most common of the autoimmune blistering diseases with an estimated incidence of 10 cases per million population (Korman, 1998). Since it is a disease primarily of the elderly, with an average onset in the eighth decade, concern has been raised that as the population is aging the incidence may also be rising (Jung *et al*, 1999). BP is characterized by the development of tense blisters of the skin, most commonly on an erythematous base. The autoimmune basis of BP was suggested by Jordon *et al* (1967) with their identification of the deposition of IgG and complement components in the skin of BP patients. Two hemidesmosomal proteins, BP180 and BP230, have been identified as the targets of the autoantibodies in BP (Stanley *et al*, 1981; Labib *et al*, 1986). A passive-transfer mouse model of BP strongly suggests that antibodies directed against the BP180 protein are of primary pathogenic importance in the development of the disease (Liu *et al*, 1993).

Large, current studies examining the mortality rate of BP patients in the US are lacking. Recent studies from Europe have shown a significant mortality in the first year following the diagnosis of BP ranging from 29% to 41% (Bernard *et al*, 1995, 1997; Roujeau *et al*, 1998; Joly *et al*, 2002; Rzany *et al*, 2002). These studies suggested that predictive factors of death in the first year were: age at onset, low serum albumin level, and pre-existing cardiovascular disease. In contrast, Venning and Wojnarowska (1992) reported a 1-y mortality of 19% and could not identify specific risk factors. One study from the US indicated a 6% mortality at 2 y (Ahmed *et al*, 1977). A more recent therapeutic study had a 5% death rate but two patients were lost to follow-up (if these were assumed dead, the rate would rise to 15%) (Fivenson *et al*, 1994). No similar recent studies have looked specifically at the mortality from this disease in the US. In this study, we retrospectively studied the mortality of all BP patients newly diagnosed at the Medical College of Wisconsin Affiliated Hospitals from 1998 until 2002.

Abbreviation: BP, bullous pemphigoid

Results

Thirty-eight patients with BP were identified. One of the patients moved out of state prior to completing 1 y of follow-up and was not included in the study. Of the 37 remaining patients, follow-up was obtained on 100% of the patients. The mean duration of follow-up for these patients was 20 mo.

The average age of our patients at the time of diagnosis was 77 y with a range from 41 to 98 y. Nineteen patients were female and 18 were male. There was no significant difference between the male and female patients with regard to age (M = 74.7 y, F = 79.6 y) or co-morbidities. Two patients were African–American and the rest were Caucasian. Cardiovascular disease was the most common pre-existing condition in our patients, identified in 59% of the patients. Diabetes was present in 15% prior to corticosteroid use, and neuropsychiatric disease in 19%. Chronic renal disease was present in 8%. In addition, a large number of patients had other autoimmune diseases, including multiple sclerosis (n = 2), thyroid disease (n = 2), and one each with pemphigus vulgaris (PV), pemphigus foliaceus (PF), inflammatory bowel disease, rheumatoid arthritis, and polymyalgia rheumatica. The patients with pemphigus had been diagnosed 9 and 25 y prior to the onset of BP and neither patient had evidence of pemphigus at the time of the diagnosis of BP. Autoantibodies to desmoglein 1 and 3 could not be detected in either patients' sera by ELISA. The

medical record of the PV patient indicated confirmation of the diagnosis by histology, direct, and indirect IF; however, archived tissue was only available for histology. Review of the histology showed suprabasilar acantholysis consistent with PV. Stored serum was available in the patient with PF, and ELISA determination from this patient at the time of the diagnosis of PF confirmed the presence of desmoglein 1 autoantibodies, but not desmoglein 3 or BP180 autoantibodies. Interestingly, both patients who had previously been diagnosed with a form of pemphigus died during the study, one 5 mo following the diagnosis of BP, the other after 2 y.

Twenty-eight patients (76%) were treated initially with systemic prednisone. The range for the highest dosage of prednisone was 10–80 mg per d. Seven patients were treated with a maximum dose of approximately 1 mg per kg per d and 17 patients with less than 0.5 mg per kg per d. Four patients' highest maximum dose was approximately 0.75 mg per kg per d. Of these patients, 22 also received a second immunosuppressive agent including mycophenolic acid (n = 5), cyclophosphamide (n = 1), azathioprine (n = 11), and dapsone (n = 7). One patient received intravenous immunoglobulin as an adjunct therapy. Two patients were treated with tetracycline and nicotinamide without steroids, one patient was treated with dapsone alone, and six patients were treated with topical steroids only.

Three patients were hospitalized when the diagnosis of BP was initially made. The average duration of hospitalization was 4.7 d. One of these patients was hospitalized three subsequent times to receive intravenous immunoglobulin therapy for his BP (Ahmed, 2001); the average stay for these additional hospitalizations was 2 d. Four additional patients were hospitalized during the study for problems other than BP. One each had bowel obstruction, pneumonia, complications of hemophilia, and exacerbation of asthma requiring hospitalization. The average duration of hospitalization for these four patients was 9 d. When examined over the entire patient base, the average initial hospitalization in our patients was 0.4 hospital days per patient. The average hospitalization throughout the course of our study for any reason was 1 hospital day per patient.

Four patients died during the first year following the diagnosis of BP (10.8%). All four of the patients who died within the first year following the diagnosis of BP were male and the mean age of the patients who died was 73 y. The characteristics of the patients who died within the first year following the diagnosis of BP are listed in Table I. Two additional patients died more than 1 y after diagnosis, one after 16 mo, and another after 24 mo of follow-up. There was one male and one female in the group that died after more than 12 mo, with a mean age of 86 y.

The results of the Kaplan–Meier analysis are shown in Fig 1. The 1-y survival probability was 88.96% (standard error 5.21%), with a 95% confidence interval of (75.6%, 94.2%).

Discussion

The first-year mortality in the patients in our study was 10.8% and overall six patients died during the study. These deaths could be due to natural causes, as a result of BP, or related to the therapy they received. Examination of the causes of death in our patients does not provide strong evidence of a relationship to their disease or therapy. Two patients died in their nursing homes at ages 96 and 98 y,

Table I. Characteristics of the patients who died during the study

Cause of death	Age/sex	Time from diagnosis to death (mo)	Co-morbidity	Treatment prior to death
Gastrointestinal hemorrhage	53/M	6	Diabetes	P 50 mg per 2.5 mg (alternate days)
			Hyperlipidemia	DAP 100 mg per d
			Hypertension	
			Alcohol abuse	
Cerebrovascular accident	81/M	3	Multiple cerebrovascular accidents	P 60 mg QOD TCN 1500 mg per d NIC 1500 mg per d
?	98/M	1	Dementia	Topical steroids
Myocardial infarction	60/M	5	Dementia	No treatment
			Cardiovascular disease	
			Pemphigus vulgaris (inactive)	
?	96/F	16	Dementia	P 10 mg QOD
Acute and chronic Renal failure	79/M	24	Pemphigus foliaceus (inactive)	P 2.5 mg QOD
			Psoriasis	
			Chronic renal failure	

P, prednisone; AZA, azathioprine; DAP, dapsone; TCN, tetracycline; NIC, nicotinamide.

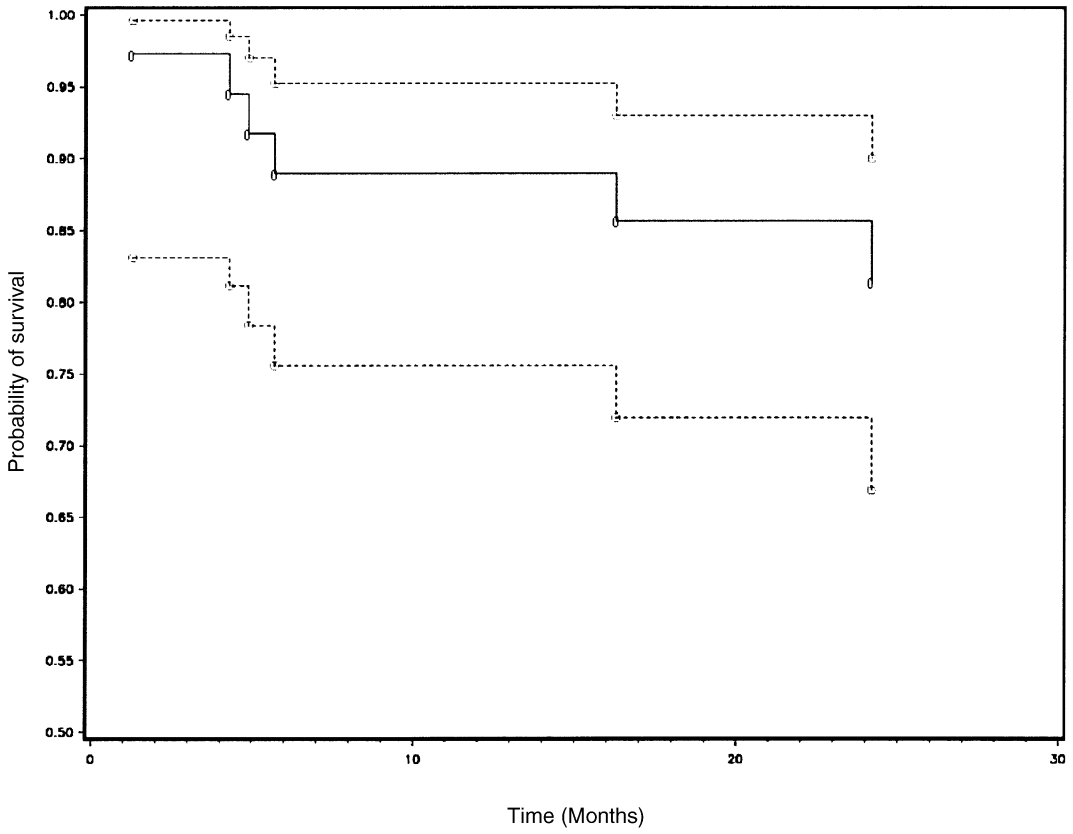

Figure 1
Kaplan–Meier curve of survival in bullous pempigoid. Four deaths occurred in the first year of follow-up and two additional at 16 and 24 mo. The 1-y survival probability of 88.96% (standard error 5.21%), indicated by the solid line. The confidence intervals (75.6%, 94.2% at 12 mo) are indicated by the dotted lines.

respectively. Both patients suffered from dementia and an autopsy was not performed on either of these patients as these deaths were deemed to be of natural causes. One patient who died of a myocardial infarction had pre-existing cardiovascular disease, mild BP, and refused treatment. The patient who died of a cerebrovascular accident had had several previous strokes and was aphasic and non-ambulatory at the time he developed BP. Although he was on prednisone at the time he died, he was not hypertensive and a relationship between prednisone and stroke has not been identified. One patient had long-standing chronic renal failure, predating the onset of this BP by many years, and died of an acute exacerbation. The use of systemic steroids could be related to gastrointestinal (GI) hemorrhage, the cause of death in the final patient. This patient, however, also had multiple other medical problems including alcohol abuse that could also contribute to the risk for GI bleeding. The mean age of death in these patients, 77.2 y, is almost identical to the current life expectancy in the US (77.2 y) (Arias and Smith, 2003).

Our study showed a significantly lower mortality in the first year following the diagnosis of BP (10.8%) than that previously reported in studies from Europe (Bernard *et al*, 1995, 1997; Roujeau *et al*, 1998; Joly *et al*, 2002; Rzany *et al*, 2002). These studies from France and Germany indicate a first-year mortality of 29%–41%. Even patients from France who were treated without systemic agents had a 24% mortality rate in the first year (Joly *et al*, 2002).

The recent study by Rzany *et al* (2002) suggests that this increased mortality in the first year may be in part attributable to higher doses of corticosteroids and increased age. Korman (1998), however, argues that because earlier studies reporting lower mortalities had comparable ages of disease onset, it is unlikely that a more advanced age accounted for the higher mortality in the French study. Korman states that a selection bias may have accounted for the higher mortality, given that the patients were seen at large referral centers. He also suggests that significant variations in survival may exist due to ethnicity, because the mortalities in several other French studies were also comparably high. Our patients were also from a tertiary care referral center and the co-morbidities in our patients were similar to those reported from France, making selection bias less likely as an explanation for the difference seen in survival. We cannot rule out differences in ethnicity or other cultural factors in the differences in survival.

The patients reported in all of these studies were recruited from academic medical centers, so are likely to represent a similar population with regard to severity and co-morbidities. But one striking difference in the management pattern of patients with BP is the rate of hospitalization in the European patients compared with our center. The standard of care in Europe is that almost all patients are initially hospitalized when the diagnosis of BP is made. The most careful assessment of hospitalization was reported by Joly *et al* (2002). The initial hospitalization in their

study averaged between 9 and 17 hospital days per patient depending on the extent of the disease and the mode of treatment. In contrast, patients are rarely hospitalized in our center for the initial treatment of BP. Only three of 37 were initially hospitalized with an average duration of 4.7 d or 0.4 hospital days per patient. During the course of follow-up, one of these patients was hospitalized three additional times for BP, in order to receive intravenous immunoglobulin therapy. The average duration of the hospitalization for these additional stays was 2 d. The cumulative hospitalization of our BP patients for any reason throughout the study was 1.0 hospital days per patient. In comparison, Joly's patients were hospitalized from 11 to 25 hospital days per patient in a study of similar duration (Joly *et al*, 2002).

The increased mortality in BP in the first year after diagnosis was reported by Roujeau *et al* (1998) to be due to sepsis (23 of 46 cases), and to a lesser extent, cardiovascular diseases (11 of 46). The cause of death was not known in 20 cases, and of the 23 who died of sepsis, 11 had concomitant pneumonitis. Joly *et al* (2002) reported similar rates of sepsis. Twenty-seven of 71 patients in whom a cause of death could be confirmed were attributed to sepsis. Twenty of those 27 had concomitant pneumonia.

Statistics on the incidence of sepsis in this country and abroad are unfortunately incomplete, largely due to differences in defining the condition and reporting parameters.

Sepsis is a contributing factor in $>$100,000 deaths per y in the United States. Approximately two-thirds of cases occur in patients hospitalized for other illnesses. Advanced age, chronic diseases, immunosuppression, indwelling catheters, and mechanical ventilation are associated with increased incidence of sepsis (Munford, 2001). A recent analysis by Angus *et al* (2001) estimated an incidence of 3.0 cases per 1000 population and 2.26 cases per 100 hospital discharges in the United States. Both incidence and mortality due to sepsis increased markedly with age in this report. Another analysis from eight academic centers in the US reported an incidence of 2.0 cases per 100 admissions (Sands *et al*, 1997). A multicenter study from 24 hospitals in France found an incidence of bacteremia and severe sepsis of 9.8 and 2.6, respectively, per 1000 adult admissions (Brun-Buisson *et al*, 1996). It was found that an independent risk factor for severe sepsis during bacteremia included age. A study from Israel found that hospital-acquired sepsis was associated with a higher mortality. In this study, 39% of cases of sepsis were hospital-acquired (Sonnenblick *et al*, 1990).

As evidenced by these reports, sepsis is largely a syndrome experienced by hospitalized patients as a complication of other conditions. Furthermore, incidence of and mortality due to sepsis apparently increases with age. The discrepancy between the reported mortality rates of BP patients across various studies could be due to rates of hospitalization (and therefore incidence of sepsis) and not directly due to age. This might explain the unusually high mortality of BP patients in Western Europe where initial hospitalization for diagnosis of BP is the norm.

Although the differences in hospitalization are intriguing we cannot rule out other geographic or ethnic differences that could account for the higher mortality in BP patients from Europe. Further careful studies of treatment modalities (including a direct comparison of ambulatory and hospitalized patients) and outcomes in these patients are needed. Our study also underscores the wide variability in the mortality of BP that may exist in difference sites. Normative data within one's own center are needed when studying these disorders until there is a better understanding of the factors that may influence survival.

Materials and Methods

Patient cohort All patients newly diagnosed with BP at the Medical College of Wisconsin Affiliated Hospitals between May 1, 1997 and September 1, 2002 were included in the study. The study was approved by the Human Research Review Committee of the Medical College of Wisconsin Affiliated Hospitals (#230-01) and was performed in adherence to the Declaration of Helsinki Guidelines. All patients had confirmation of the diagnosis of BP by histology and immunofluorescent testing. All patients demonstrated autoantibodies against BP180 and/or BP230, which was previously performed in these patients as part of another research study (Dimson *et al*, 2002). The age at onset, method of treatment (including the highest dose of prednisone used), pre-existing comorbidities, days of initial and/or subsequent hospitalizations, and the reasons for hospitalization were recorded. The last follow-up or date of death was also identified. If a patient died, the medications they were receiving for BP at the time of death were noted. Patients were followed for a minimum of 1 y or until the time of death.

Statistical analysis The Kaplan–Meier method was used to estimate the survival probability and the survival standard error. The log-transform method was used to estimate confidence intervals for the survival probability. This analysis was performed with SAS statistical software (The SAS Institute, Cary, North Carolina).

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