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Specific Causes of Death in Patients with Bullous Pemphigoid as Measured by Death Certificate Data: A Retrospective Cohort Study

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Abstract

Background—While patients with bullous pemphigoid (BP) have increased mortality rates compared with age-matched counterparts, the specific causes of death have not been evaluated systematically. We sought to characterize the causes of death in patients with BP as recorded by death certificate and compare to age- and location-matched control death data.

Methods—This was a retrospective cohort analysis in a large tertiary referral center. Twenty-seven participants who had a confirmed antemortem diagnosis of BP, were residents of Olmsted County, Minnesota, and had died between January 1, 1999 and January 1, 2009 met the criteria required to be included in the study. Underlying cause of death and multiple cause of death data from the study population were compared to data from the CDC for a control group matched by age and geographic location of origin by ICD-10 block and specific ICD-10 codes.

Results—Comparison of specific ICD-10 codes revealed increased rates of sepsis ($p = 0.031$), dementia ($p = 0.049$), and major depressive disorder ($p = 0.005$) in the study group. Taken together, the ICD-10 codes for infections were more frequent contributors to death in the study group ($p = 0.035$).

Conclusion—Clinicians should be mindful of the contributors to death in patients with BP and could consider screening for mental health issues, educating patients of early symptoms of sepsis, and minimizing risk factors for infection.

Introduction

Bullous pemphigoid (BP), the most common autoimmune bullous dermatosis,[1] is characterized by a humoral response to the BP230 and BP180 self-antigens. Both antigens are components of the adhesion complex, which secures epidermal basal cells to the underlying basement membrane. The disease manifests as pruritic, tense bullae and urticarial plaques in the elderly population.

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Recent studies have noted that the incidence of BP is increasing.[2,3] Many have also reported an increased rate of mortality compared with the age- and sex-adjusted general population,[2,4] although this finding has not been reported consistently.[5] In the United States, the 1-year-mortality rate for patients diagnosed with BP was reported to be 23%.[5] Common comorbidities and associated medical conditions have also been studied. Several studies attribute the increased mortality to advanced age, associated medical conditions, and hospitalization instead of disease-specific factors.[6,7] Others suggest that several degenerative neurologic diseases and stroke may be associated with BP.[4,8,9,10]

While many studies have addressed the incidence and rate of mortality, we are aware of scant literature that has addressed the specific causes of mortality in patients with BP. The purpose of the present study is to characterize the underlying cause of death and multiple causes of death amongst patients seen at Mayo Clinic with BP from Olmsted County, Minnesota via retrospective chart and death certificate review.

Materials and Methods

This was a retrospective cohort study with chart and death certificate review. Because all patients were deceased, this project was deemed not to require Institutional Review Board approval. This study was supported financially by Mayo Clinic Department of Dermatology funds and was made possible by the Rochester Epidemiology Project (Grant Number R01 AG034676 from the National Institute of Aging.)

Deceased patients with an antemortem diagnosis of BP were included in the study. Inclusion criteria were the following: patient deceased between 1999 and 2009; resident of Olmsted County, Minnesota with death certificate; and diagnosis of bullous pemphigoid based on clinical, histological and immunological criteria. To ensure accuracy in the diagnosis of pemphigoid, a meticulous chart review was performed to ensure that clinical features of pemphigoid were present, and clinical features of other mimicking diseases were absent.[11] In addition to compatible clinical findings, 2 of 4 of the following pathologic findings were required: (i) skin histology consistent with bullous pemphigoid (eosinophilic subepidermal blister, urticarial tissue reaction, and/or eosinophilic spongiosis.) (ii) Direct immunofluorescence with linear C3 +/− IgG (iii) Positive indirect immunofluorescence (iv) positive ELISA for BP180 and/or BP230 autoantibodies. Therefore, each patient had evidence of tissue or serum circulating autoantibodies directed against the basement membrane zone.

Patients were identified by a search through the Mayo Clinic patient record database. Death was confirmed using the Rochester Epidemiology Project (REP) death browser database. Twenty-seven deceased patients from Olmsted County met criteria and were included in the study. No eligible patients were excluded.

Diagnostic findings of BP and demographic information were recorded from electronic medical charts. Underlying cause of death (UCD) and multiple cause of death (MCD) data were obtained from the death records from the REP death browser database. The CDC defines UDC as “the disease or injury that initiated the train of events leading directly to

death, or the circumstances of the accident or violence, which produced the fatal injury."[12] Up to 20 additional factors contributing to death (MCD) are also reported on the standard US death certificate. We evaluated both UCD and MCD data, since it is known that both should be evaluated together in order to establish the most accurate picture of the contributing causes of death.[13] For standardization, the UCD for each subject was also listed in the MCD category. Each ICD-10 code documented in the death certificates was sorted into ICD-10 blocks for data analysis for both UCD and MCD.

UCD and MCD data from the Center for Disease Control and Prevention mortality database (http://wonder.cdc/gov/) was obtained for a group of subjects matched by age and geographic location in Olmsted County from 1999 to 2009 to serve as our control group.[14] Mortality data from patients with BP were compared to CDC data by ICD-10 block and specific ICD-10 code for both UCD and MCD.

MCD data was evaluated similarly to UCD with one important difference. While each patient was designated with one UCD code, many MCDs were listed as contributing factors in each death certificate. Therefore, MCD data were compared by proportions of all MCD codes, as opposed to by proportions of all patients. For example, the death certificates of our 27 patients contained 27 ICD-10 codes for UCD and a total of 107 codes for MCD. After subtracting our patient group from the control group, the CDC reported 6,802 UCD and 25,285 MCD codes representing 6,802 patients. The average number of MCD entries per subject in the study population was 4.0 with a control average of 3.7. Proportions were compared by ICD-10 block and specific ICD-10 codes.

The ICD-10 is structured to organize codes pertaining to infection into the block A00-B99; however, many causes of death with underlying infection are listed by organ system. Therefore, in order to further evaluate infection, all ICD-10 codes with infectious etiology were compared to all listed MCD mortality with underlying infection. One code in the study group, K83 (Cholangitis), was excluded because the CDC did not include data for cholangitis due to its rarity.

Comparisons of causes of death between the study and control groups were evaluated using chi-square and Fisher exact tests. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). All tests were two-sided and p-values <0.05 were considered statistically significant.

Results

In all, there were 27 subjects with confirmed BP who met the criteria of our study [22 (81%) were female]. The median age of death was 89.6 years and the mean was 88.5 (SD 7.55). The age range at death was 66.8 to 97.7 years old. The median time from diagnosis of BP to death was 2.46 years and the mean was 3.06 years (SD 2.55).

Underlying cause of death and multiple causes of death were compared between patients with bullous pemphigoid and CDC data. Results were recorded in Table 1–4.

Comparison of UCD data revealed a significant difference in the category of neoplasms, with the control population experiencing more neoplasms than the study group ($p = 0.043$). When specific ICD-10 codes were reviewed, we found no statistically significant difference between the groups.

Comparison of MCD data revealed differences between several ICD-10 blocks. The control group had a higher rate of neoplasms ($p = 0.025$) and diseases of the circulatory system ($p = 0.026$). Conversely, a higher rate of mental and behavioral disorders ($p = 0.002$), diseases of the digestive system (0.025), and diseases of the genitourinary system (0.025) was observed in the study group.

Specific MCD differences of statistical significance were the following: Sepsis, A41.9 ($p = 0.031$); Dementia, F03 ($p = 0.049$); Major depressive disorder, F32.9 ($p = 0.005$).

Of the 4 patients with sepsis, the underlying causes were: cholangitis, pneumonia, urinary tract infection and unknown origin. Only one of these patients was receiving immunosuppressant medication for BP at time of death.

Comparison of all infections as MCD is listed in Table 5. A specific difference of statistical significance was noted for infection as a contributing cause of death ($p = 0.035$).

Discussion

This study contributes to the current understanding of factors contributing to death in patients with BP. Several MCD ICD-10 blocks were noted to be of significant difference between the study and control group which include: mental and behavioral disorders, disease of the circulatory system, disease of the digestive system, and disease of the genitourinary system. Additionally, increased rates of sepsis, infection, dementia and major depression as contributory causes of death were noted amongst the study group when specific ICD-10 codes were compared against the control group.

The association of BP and neurologic disease has been studied extensively. A recent prospective study found degenerative neurologic disease to be an independent risk factor for the development of BP.[15] Importantly, major depressive disorder was a statistically significant cause of death upon review of the data. Although a previous diagnosis of dementia may be a confounder for these findings, the presence of BP among other immunobullous disease has been documented to decrease quality of life in patients with BP.[16,17] Therefore, quality of life and mental health should be an important consideration in the management of these patients.

The association of sepsis and BP has been studied and remains an area of controversy.[5,18] The present study systematically compared BP patients to CDC control data which demonstrated an increased rate of infection in the study group. BP, as well as other autoimmune bullous dermatoses, is associated with increased risk for infection.[19] The elevated rate of infection and septicemia as MCD implies that infection control is an important consideration in the management of patients with autoimmune bullous disease.[19]

The association between BP and disease of the circulatory system, especially stroke, has been discussed extensively.[4, 8, 9,10] Such findings may be related to chronic inflammation and corticosteroid use as contributing factors in atherogenesis.[20] Increased disease of the circulatory system was observed in the control population. Our findings are not consistent with previous research. This may be the result of evaluating all diseases of the circulatory system including diagnoses such as hypertension, stroke and myocardial infarction in the same ICD-10 block. When compared individually, no significant difference was noted between the groups for disease of the circulatory system.

The study group demonstrated a lower rate of neoplasms and a higher rate of digestive and genitourinary system disease, as compared to the control. Upon further examination of the specific ICD-10 codes, five of eight recorded MCD codes were suggestive of renal failure (N17.8, N18.9(2), N19(2)). No apparent disease pattern was noted amongst ICD-10 codes for digestive disease. Why these trends exist was unclear but would be worthy of future study.

This study has several limitations. First, this was a retrospective study of a small number of patients, the majority of whom being women. Since the United States does not have a national immunobullous disease database, the available number of patients in our study was limited. Prior reports that have included large numbers of patients with BP have looked at rates of mortality but not causes of mortality. Our study is unique in that it evaluated a population of BP patients with death certificate data and, therefore, is the most detailed mortality information reported, to date. Additionally, the validity of death certificate data has been questioned previously,[21] because cause(s) of death may be incorrectly reported on death certificates. However, a recent study demonstrated that death certificate data from the REP was sufficiently sensitive and specific to evaluate certain mortality-based outcomes.[22]

Studying patients from Olmsted County, Minnesota, has several unique advantages for this research project, including exceptional longitudinal subject follow-up, access to full chart access across specialties, excellent information on mortality and complete follow-up capability for mortality with REP death data.[23] Additionally, age and sex-specific mortality rates from Olmsted County have been found to be similar to state and national mortality rates.[24]

The relationship between BP and increased mortality rate has been the subject of numerous studies; however, reports of cause of death data are scarce in the literature. We have demonstrated that there is a significant association between BP and dementia, infection, sepsis and major depression as contributors to death. Future larger studies are needed to confirm these findings.

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Table 1

UCD as reported by ICD-10 block for subjects in the study and control groups

No UCD data was recorded in the study or control group in the following ICD-10 blocks: H00-H57 Diseases of the Eye and Adnexa; H60-H93 Diseases of the ear and Mastoid Process; O00-O91 Pregnancy, childbirth, puerperium; P00-P96 Certain conditions originating in the perinatal period; Q00-Q99 Congenital malformations, deformations, and chromosomal abnormalities; R00-R99 Symptoms, signs and abnormal clinical findings and lab.; U00-U99 Codes for special purposes; and V01-Y89 External causes of morbidity and mortality.

	ICD-10 Block	BP UCD %	(N)	CDC UCD %	(N)	p - value
A00-B99	**Certain Infections and Parasitic Disease**	3.70%	1	1.21%	82	0.28
C00-D48	**Neoplasms**	7.41%	2	24.08%	1,638	**0.043**
D50-D89	**Disease of the Blood and Blood Forming Organs and Certain Disorders Involving the Immune System**	0%	0	0.28%	19	1.0
E00-E88	**Endocrine, Nutritional and Metabolic Diseases**	3.70%	1	2.25%	153	0.46
F01-F99	**Mental and Behavioral Disorders**	18.52%	5	8.67%	590	0.08
G00-G98	**Diseases of the Nervous System**	7.41%	2	6.85%	466	0.71
I00-I99	**Diseases of the Circulatory System**	29.63%	8	33.71%	2,293	0.65
J00-J98	**Diseases of Respiratory System**	11.11%	3	11.29%	768	1.0
K00-K92	**Diseases of the Digestive System**	7.41%	2	3.25%	221	0.22
L00-L98	**Diseases of the Skin and Subcutaneous Tissue**	0%	0	0.19%	13	1.0
M00-M99	**Diseases of the Musculoskeletal and Connective Tissue**	0%	0	1.10%	75	1.0
N00-N98	**Disease of the Genitourinary System**	3.70%	1	2.25%	153	0.46
R00-R99	**Symptoms, Signs and Abnormal Clinical Findings and Lab. NOS**	0%	0	0.69%	47	1.0
V01-Y89	**External Causes of Morbidity and Mortality**	7.41%	2	4.18%	284	0.31
Total			27		6802	

Table 2

UCD as reported by individual ICD-10 codes for subjects in the study and control group.

	Specific ICD-10 codes	BP UCD %	(N)	CDC UCD %	(N)	p - value
F03	**Unspecified Dementia**	18.52%	5	8.09%	550	0.063
I25.9	**Chronic Ischemic Heart Disease, Unspecified**	11.11%	3	9.04%	615	0.73
Total			27		6802	

Table 3

MCD as reported by ICD-10 block for subjects in the study and control groups

No MCD data was recorded in the study or control group in the following ICD-10 blocks: O00-O91 Pregnancy, childbirth, puerperium; P00-P96 Certain conditions originating in the perinatal period; and U00-U99 Codes for special purposes.

	ICD-10 Block	BP MCD %	(N)	CDC MCD %	(N)	p - value
A00-B99	**Certain Infections and Parasitic Disease**	3.74%	4	1.79%	452	0.13
C00-D48	**Neoplasms**	3.74%	4	10.37%	2623	**0.025**
D50-D89	**Disease of the Blood and Blood Forming Organs and Certain Disorders Involving the Immune System**	0.93%	1	1.14%	287	1.0
E00-E88	**Endocrine, Nutritional and Metabolic Diseases**	8.41%	9	6.14%	1553	0.33
F01-F99	**Mental and Behavioral Disorders**	13.01%	14	5.97%	1510	**0.002**
G00-G98	**Diseases of the Nervous System**	2.80%	3	4.04%	1022	0.80
H00-H57	**Diseases of the Eye and Adnexa**	0%	0	0.29%	73	1.0
H60-H93	**Diseases of the ear and Mastoid Process**	0%	0	0.04%	11	1.0
I00-I99	**Diseases of the Circulatory System**	26.17%	28	36.59%	9251	**0.026**
J00-J98	**Diseases of Respiratory System**	10.28%	11	11.30%	2857	0.74
K00-K92	**Diseases of the Digestive System**	7.48%	8	3.27%	827	**0.025**
L00-L98	**Diseases of the Skin and Subcutaneous Tissue**	0.93%	1	0.38%	96	0.34
M00-M99	**Diseases of the Musculoskeletal and Connective Tissue**	1.87%	2	2.53%	640	1.0
N00-N98	**Disease of the Genitourinary System**	9.35%	10	4.73%	1197	**0.025**
Q00-Q99	**Congenital Malformations, Deformations, and Chromosomal Abnormalities**	0%	0	0.13%	32	1.0
R00-R99	**Symptoms, Signs and Abnormal Clinical Findings and Lab. NOS**	1.87%	2	4.31%	1090	0.33
S00-T98	**Injury, Poisoning and Certain Other Consequences of Other Causes**	4.67%	5	3.50%	885	0.43
V01-Y89	**External Causes of Morbidity and Mortality**	4.67%	5	3.48%	879	0.43
Total			107		25285	

Table 4

MCD as reported by individual ICD-10 codes for subjects in the study and control groups.

	Specific ICD-10 codes	BP MCD %	(N)	CDC MCD %	(N)	p - value
A41.9	**Sepsis, Unspecified Organism**	3.74%	4	1.10%	277	**0.031**
F03	**Unspecified Dementia**	8.41%	9	4.26%	1076	**0.049**
F32.9	**Major Depressive Disorder, Single Episode**	3.74%	4	0.63%	160	**0.005**
I10	**Essential (Primary) Hypertension**	4.67%	5	5.80%	1467	0.62
I25.1	**Atherosclerotic Heart Disease of Native Coronary Artery**	3.74%	4	6.05%	1529	0.32
I50	**Heart Failure**	3.74%	4	4.05%	1023	1.0
J18.9	**Pneumonia, Unspecified Organism**	4.67%	5	2.81%	710	0.23
Total			107		25285	

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Table 5

MCD as reported by individual ICD-10 codes pertaining specifically to infectious etiology for subjects in the study and control group.

	Specific ICD-10 Codes (Infection)	BP MCD %	(N)	CDC MCD %	(N)	P-Value
J18.9	**Pneumonia, Unspecified Organism**	4.67%	5	2.81%	710	0.23
A41.9	**Septicaemia, Unspecified Organism**	3.74%	4	1.10%	277	**0.031**
N39.0	**Urinary Tract Infection, Site Not Specified**	1.87%	2	0.72%	183	0.18
J18.0	**Bronchopneumonia, Unspecified**	0%	0	0.33%	83	1.0
I38	**Endocarditis, Valve Unspecified**	0%	0	0.26%	66	1.0
A04.7	**Enterocolitis due to Clostridium difficile**	0%	0	0.09%	22	1.0
L03.9	**Cellulitis, Unspecified**	0%	0	0.06%	16	1.0
B18.2	**Chronic Viral Hepatitis C**	0%	0	0.06%	14	1.0
A49.0	**Staphylococcal Infection, Unspecified**	0%	0	0.05%	12	1.0
A49.9	**Bacterial Infection, Unspecified**	0%	0	0.04%	10	1.0
B17.1	**Acute Hepatitis C**	0%	0	0.04%	10	1.0
I33.0	**Acute and Subacute Infective Endocarditis**	0%	0	0.04%	10	1.0
K83	**Cholangitis**	0.93%	1		Not reported	NA
Total		11.21%	12	5.59%	1413	**0.012**
Total minus K83		10.28%	11	5.59%	1413	**0.035**
Total			107		25285	